5432924

CENTRAL INTELLIGENCE AGENCY

INFORMATION REPORT

S-E-C-R-E-T
NOFORN [redacted] 25X1

COUNTRY	East Germany	REPORT [redacted]	25X1
SUBJECT	VEB Schering Adlershof Pharmaceutical Preparations	DATE DISTR.	16 February 1956
		NO. OF PAGES	1 25X1
DATE OF INFO.	[redacted]	REQUIREMENT	[redacted]
PLACE ACQUIRED	[redacted]	REFERENCES	[redacted]
DATE ACQUIRED	[redacted]		

THE SOURCE EVALUATIONS IN THIS REPORT ARE DEFINITIVE.
THE APPRAISAL OF CONTENT IS TENTATIVE.
(FOR KEY SEE REVERSE) 25X1

[redacted] 25X1

[redacted] 25X1

[redacted] pharmaceutical products manufactured by VEB Schering Adlershof. [redacted] 25X1

A. Ampoules of Calcium Thiosulphate "Schering" (Tecesal). (10 pages)

B. Acetylcholine - Biocatalyst of the Parasympathetic Nervous System, Vaso-dilator. (16 pages) 25X1

C. Alluval - Alpha-bromisolvalerylcarbamide Sedative and Alluval Forte - Alpha-bromisolvalerylcarbamide with Diethylbarbiturate of Sodium Sedative, Hyonotic, Spasmolytic. (10 pages)

D. Supracid (Combination of Superior Sulphonamides). (13 pages)

E. Gentiaverm for the Chemotherapy of Oxyuriasis. (9 pages)

F. Pernaemyl Forte - Highly Concentrated Liver Preparation (with vitamin B-12). (20 pages)

[redacted] 25X1

S-E-C-R-E-T
NOFORN [redacted] 25X1

STATE	X	ARMY	X	NAVY	X	AIR	X	FBI		AEC						

(NOTE: Washington distribution indicated by "X"; Field distribution by "#".)

SECRET NOFORN

ATTACHMENT [redacted] 25X1

D

S U P R A C I D

Equal Shares of

2-(p-aminobenzolsulphonamide)-4-methyl-pyrimidine
and p-aminobenzolsulphonamide-ethyl-thiodiazol

Combination
of ~~super~~-sulphonamides
superior

SECRET NOFORN

S U P R A C I D

Generals

The discovery of sulphonamides and antibiotics signified a subverting progress of the whole medicine. Prior to such epoch-making knowledge it had not been possible to obviate infections with effective drugs. Many of previously feared infections now lost their fright upon the possibility of effective and quick-acting treatment. While the antibiotics kill the germs of diseases the sulphonamides arrest the effect of the p-aminobenzoic acid existing in any bacterium and required for its metabolism, thus paralysing the bacterium, and let it fall a victim of the body's powers of resistance.

Proceeding from sulphanilamide, the base of the sulphonamides, the synthesis of numerous sulphonamides of partially quite different effects followed very soon. Out of the great number of compounds a small group of superior sulphonamides turned out prominent qualities, namely especially good compatibility and high efficiency. Sulphonamides are eliminated through the kidneys. In the beginning of the era of sulphonamides the unhappy juncture of bad solubility and delayed elimination of the sulphonamide occasionally entailed its crystallization within the kidney, thus causing renal injuries. Our SUPRACID excels, among others, in the impossibility to injure the kidneys in this manner.

It was understood very soon that the individual sulphonamides differ in the speed of their resorption and elimination. These two facts are of main importance as to therapeutical effect and compatibility. Easily resorbable sulphonamides are acting quicker than the difficultly absorbable ones which, however, take longer lasting effect. - For any sulphonamide a certain concentration in blood, the so-called concentration level, is required. The level of SUPRACID must amount at the least to 10 milligrams within 100 c.cm the SUPRACID at lower level not paralysing the bacteria sufficiently; individual, weak bacteria, however, may go on suffering from paralysation but resistent ones will get immune from the agent as soon as the concentration level of sulphonamide decreases below the required limit; in this way the drug becomes ineffectual, and the patient is injured instead of being availed.

The combination of an easily absorbable agent of quick elimination with a more difficultly absorbable one of delayed elimination, both, of course, of convenient, therapeutical efficiency, resulted in the discovery of the principle of "Sulpho-summation". In this manner the combined preparations ensued differing considerably from single sulphonamides, and that particularly in:

1) increased therapeutical efficiency by quick formation of high levels of concentration in blood, liquor, and tissues which remain for a long time on their heights quickly arrived at;
2) increased width of effect by summing up the different efficiencies of the individual components;
3) improved compatibility in consequence of easy solubility within urine, i.e. dislodging of the danger of formation of concretions, and that by combining a difficultly soluble sulphonamide and an easily soluble one, thus improving the solubility of the difficultly soluble component in urine;
4) neglected night-medication as, due to the existence of an agent of delayed elimination, also during the night a sufficiently high concentration level in blood, liquor, and tissues is maintained. In severe cases only a nocturnal treatment might be required.

Since a couple of years the combination of globucide and sulphomethylpyrimidine has turned out excellently; we are producing this combination in shape of SUPRACID.

SUPRACID means:

Quick action

High and constant concentration level in blood, liquor, and tissues

Superior therapeutical efficiency

Excellent compatibility on the part of kidneys

Prominent, general compatibility, also on the part of the stomach.

Pharmacology

SUPRACID is a combination of equal shares of sulphomethylpyrimidine and sulphoethylthiodiazol. Each tablet of SUPRACID contains 0.25 grams, the ampoulle (10 c.cm of a totally 20 percent aqueous solution of the corresponding sodium salts) 1 gram each of the two components.

25X1

Sulphomethylpyrimidine (methylpyrimal, pyrimal-M)

- Chemische Formeldarstellung! -

is, according to the constitutional formula, a 2-(p-amino-benzolsulphonamide)-4-methyl-pyrimidine. Upon peroral application sulphomethylpyrimidine is resorbed very soon, thus quickly entailing high concentration of level in blood. After one peroral medication of 3 grams of SUPRACID in 8 cases the medium concentration of blood amounted, after 2 hours, to 12.8 mg%, and after 4 hours the maximum of 13.8 mg% was reached. Then the content slowly decreased again arriving, after 24 hours, at an average value of 5.9 mg% (according to Schönfeld-Klimmig (15)). The elimination of sulphomethylpyrimidine is proportionally slow. From this fact a longer lasting high and constant level of blood, liquor, and tissues results. Slow elimination, however, is ensued by reinforced acetylation in the body. Sulphonamides are acetylated in the body in different quantities. The therapeutically ineffectual acetyl-sulphonamides, of course, are in general of relatively difficult solubility, and may cause the feared formation of concretions, and that by crystallising in the kidney, the organ of elimination of sulphonamides, thus entailing serious complications.

But sulphomethylpyrimidine, on the contrary, excels in easy solubility of the acetyl-compound so that renal complications must be hardly expected, particularly when sufficient care is taken for alkalising the urine by ample supply of fluid, and, if necessary, by additional medication of bicarbonate of soda.

Out of free sulphomethylpyrimidine at room-temperature 87 mg are dissolved in 100 grams of serum.

Out of acetylated sulphomethylpyrimidine, on the contrary, at room-temperature the following quantities are dissolved, according to the corresponding p_H-environment:

p_H 5: 22 mg%
p_H 6: 45 mg%
p_H 7: 115 mg%
p_H 8: 304 mg%

Consequently the acetylated sulphomethylpyrimidine is of excellent solubility all the more the extent of acetylation of sulphomethylpyrimidine in human urine amounts to about 58 %.

NOFORN

25X1

The p_H-value of a 20 percent aqueous solution of sulphomethylpyrimidine-sodium amounting to 10.7 the advantage of the good solubility is proved; consequently there is, in spite of highest doses, no reason for fright at the formation of renal concretions.

Sulphoethylthiodiazol

(- Chemische Formeldarstellung! -)

For years past the 2-(4'-aminobenzolsulphonamido)-5-ethyl-1,3,4-thiodiazol as globucide has prominently turned out in therapy, due to its efficiency and excellent compatibility. It is quickly resorbed, too, and, on the contrary to the sulphomethylpyrimidine, also quickly eliminated again. Therefore the extent of acetylation within the body is kept small (see page 8). The acetyl-globucide, furthermore, and on the contrary to the acetyl-compounds of the major part of other sulphonamides, being of same, easy solubility as the above-mentioned sulphomethylpyrimidine also globucide does not entail any formation of renal concretions.

Solubility of acetylated sulphonamides at changed p_H-value:

(- Kurvendiagramm! -)

Red = Globucide
Brown = Sulphomethylpyrimidine
Blue = Sulphonilamide
Green = Sulphothiazol
Yellow = Sulphopyridine

Solubility of <u>acetyl</u>-globucide at different p_H-values:

p_H 5: 14 mg%
p_H 6: 54 mg%
p_H 7: 392 mg%
p_H 8: 880 mg%

Solubility of <u>free</u> globucide in serum at room-temperature:
239 mg%

Extent of acetylation in human urine: about 8 percents.

p_H-value of a 20 percent aqueous solution of the sodium salt:
7.3

Supracid

Globucide and sulphomethylpyrimidine are preminently supplementary one to the other as to their qualities ; for this reason the combination of both agents must result in a preparation which is superior in respect of efficiency and compatibility. Practice has certified that the co-operation of globucide and sulphomethylpyrimidine asserts the principle of sulpho-summation, thus entailing substantially increased therapeutical efficiency and compatibility. Agents of quick elimination (globucide) and such of delayed elimination (sulphomethylpyrimidine) secure a quick and steeply ascending increase of the level of blood, liquor, and tissue, and proportionally long-lasting maintenance of the conditions achieved

(- Kurvendiagramm! -)

- Hours after Medication -

Conditions of level of blood upon one peroral medication of 3 grams of SUPRACID (cp. curve of level of blood on page 9).

The curve distinctly shows the quick rise exceeding the required minimum level of blood of 10 mg%; the therapeutically effective lower limit is, in spite of the single medication, reached again not earlier than after 6 hours. Both features distinguish SUPRACID as a modern, combined preparation which, of course, during therapy is medicated more than once (cp. curve on page 8).

Since both components are eliminated at different times the test of the kidneys is smaller than when using only one sulphonamide. In this connection importance should be attached to the fact that, when combining two opposite sulphonamides, the conditions of solubility of the eliminated products in urine become more advantageous than under use of only one of the two components.

Concentration of Sulphonamide in Serum upon One Medication of 4 grams:

(- Kurvendiagramm! -)

Orange = SUPRACID
Red = Globucide
Brown = Sulphomethylpyrimidine

t/-- Hours

25X1

25X1

Free SUPRACID is in serum and at room-temperature soluble in value of 296 mg%. But the solubility of acetylated SUPRACID is approximately corresponding to that of acetylated sulphomethylpyrimidine the share of acetyl-globucide not being important (cp. page 6).

The p_H-value of a 20 percent aqueous solution of supracid-sodium is 9.4. The lower limit of the therapeutically required level of blood is 10 mg%.

Upon only one medication of 4 grams per os this value is reached already after one hour and a half. After 24 hours still 5 mg% could be proved (according to Schwartz (18)) (cp. curve on page 9). In human urine SUPRACID is acetylated to the extent of 32 percents.

(- Kurvendiagramm! -)

Orange = SUPRACID
Green = Sulphothiazol
Blue = 2.4-dimethylpyrimidin

------ Hours

Sulphonamide-level in serum upon one peroral medication of 4 grams.

(- Kurvendiagramm! -)

1st 2nd 3rd 4th 5th 6th 7th 8th day

SUPRACID-level of blood after medication of 63 grams within 7 days, and that 12 grams on the first day which dose then was gradually reduced by 1 gram per day. Repeated medications of sulphonamide, therefore, tremendously increase the level of blood.

(- Graphik! -)

Improvement of solubility by combination.

In human serum at room-temperature the following quantities are dissolved:

Brown	= Sulphomethylpyrimidine	87 mg%
Red	= Globucide	239 mg%
Orange	= SUPRACID	296 mg%

25X1

SECRET NOFORN

Virtues and effect

Numerous publications prove the optimal efficiency and compatibility of the combination of globucide and sulphomethylpyrimidine as present in SUPRACID.

Jüptner (9) reports that the combination as present in SUPRACID excellently turned out in the line of gynaecology. Where other sulphonamides had failed SUPRACID resulted in unobjectionable successes; in this connection the treatment of 112 feverish abortions left special impression. König (12) confirms the good successes in the line of gynaecology. He points out the good compatibility at a dosage of 10 grams per day which were medicated in single doses every four hours without increasing the supply of fluid. Especially good effect he was able to observe also when treating feverish abortions and pyelitis. Inflammations of the endometrium were not influenced; the spreading of germs, however, was prevented.

Beyond the third month of life complications on the part of the liver, kidneys, or the formation of methaemoglobin with severe cyanosis, as may occur when medicating other sulphonamides, were not observed in any case. (the special care to be taken during the first three months of life is discussed in details on page 13.) The new combination SUPRACID succeeded also in the event of other sulphonamides being incompatible on the part of the stomach.

In the line of internal medicine the new combination-drug excellently stood its test of confirmation to largest extent.

Hückstädt (8) reports on successes when treating 20 lobar pneumonias, 13 bronchopneumonias, 5 cases of otitis, 2 scarlatinal anginas, 2 cases of scarlatinal otitis, 15 cases of scarlatinal lymphadenitis, 4 cases of coli-pyelitis, 1 thrombophlebitis, 1 erysipelas, several suppurative skin-diseases, and 2 cases of coli-cholangitis. In this connection importance should be attached to the fact that globucide is concentrated within bile in such a way that globucide and, consequently, SUPRACID may be designed as drugs of selection for bile-infections.

Bahlmann (1) brings into special prominence the good success when curing lobar pneumonia. He points out that even at high dosage any alkalizing of urine was neglected without any demand for considerably increased supply of fluid. Neither

25X1

ATTACHMENT TO EOB - 11/11 2

E

G E N T I A V E R M

For the Chemotherapy of Oxyuriasis

25X1

G E N T I A V E R M

For the Chemotherapy of Oxyuriasis

Biology

The pin-worms, also named thread-worms, (oxyuris vermicularis or enterobius vermicularis) are prevalent in the small and the large intestine, particularly in the terminal intestine, frequently in the appendix. The female leaves the anus, deposits there 10000 to 12000 ova, and dies. The male dies already in the intestine after copulation. If the number of oxyuris existing in intestine is very small the pinworms are always protruding up to the centre of bulk, saying that they never can be proved by examining the stools merely from outside. In such events the eosinophilia of the blodd-picture may be considered as important indication.

Any anal or vaginal itching arouses a suspicion of oxyuriasis. The microscopic examination then will clarify the matter.

The fundamental condition for a successful worm-cure is the interruption of the way from anus to the mouth. For this purpose the affected patient has to wear, at the least during night, waterproof slips or knickers, and to keep the anal region covered, up to finished seventh year of age, with a paste of aluminium acetate, and, beyond this age, with a paste of 5 percent, white precipitate. Up to now we have desisted from the use of such pastes our GENTIAVERM being an absolutely and reliably acting vermifuge. The patients, however, not treating the matter seriously enough we have decided to meet this indifference by recommending a paste. - The great number of vermifuges and treatment propagated up to now proves their untrustworthiness. Aluminium acetate as formerly used nearly everywhere is, according to Ehrhardt (2) (Heidelberg) hardly acting on oxyuriasis. Kudicke (5) pointed out the high efficiency of gentian (crystal) violet on other sorts of worms; This agent, therefore, was used for oxyuriasis, and excelled in conspicuous successes.

Epidemiology

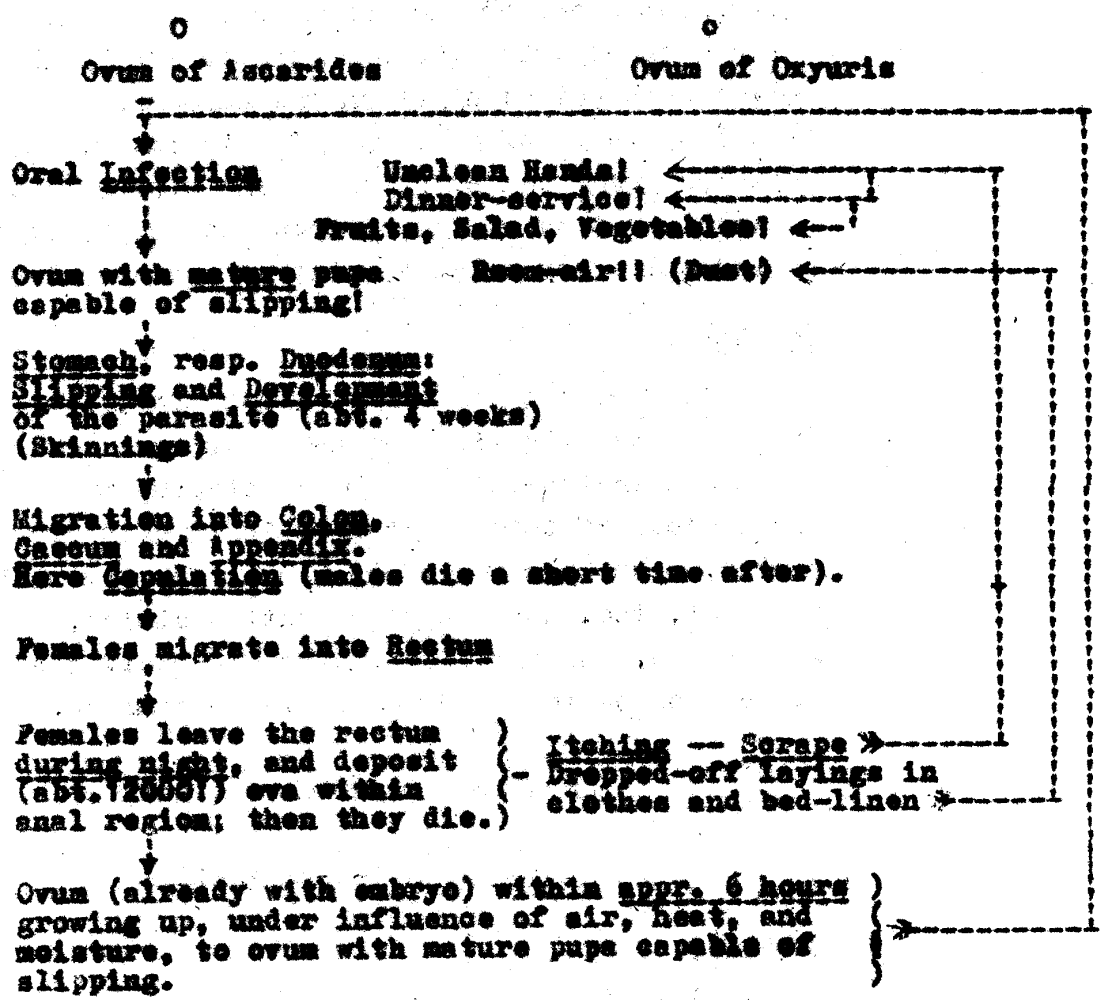
Leick (6) found, in course of 1000 autopsies, an affection with oxyuris in value of 43.2 percents. Even this high figure is too low inasmuch as Hamak (3) stated that 90 percents of

all children up to the 16th year of their life are infected with oxyuris, and Brumpt (1) even increases this figure up to 96.6 percents.

Oxyuris Vermicularis L.
(Enterobius vermicularis)

Male: 3 to 5 mms length. Female: 8 to 12 mms length.
From each female about 10000 to 12000 ova; ova oblong-ovate, almost colourless, thick and smooth shell,
length: 40 to 60 µ, width: 30 µ

For Drawing a Parallel:



Macroscopic Proves

Adult persons take, at night or early in the morning, 30 grams of Glauber's salt on an empty stomach and dissolved in water in order to discharge the intestine at the least four times;

oxyuris, if any, will be found in 3rd and4th, always liquid discharge. Owing to the observation that the rectum may be free from oxyuris which, in spite of this, at the same time are abundantly existing in the small intestine at grown up people beyond the 16th year of their life any proof cannot be executed unless upon intensive relief of the bowels as described hereabove.

It is clear that stools evacuated by means of Glauber's salt have to be discharged into a dish-like vessel or similar.

Microscopic Proof

When adhering to correct procedure the modern, microscopic control of stools will never fail. As to children a light smear from exterior anal skin is microscopically examined for ova of oxyuris; the same can be done with a slightly salved swab put at night on the anus and fastened to it reliably by means of a stripe of sticking-plaster. The most reliable proof can be given by the stripe of cellophane. - In consideration of the environment or physical symptoms eosinophilia may valuably hint at intestinal parasites.

Chemistry

The modern therapy of oxyuriasis prefers dye-stuffs obtained from methyl-derivatives of p-rosaniline. Especially penta and hexamethyl-p-rosaniline are playing an important part. The mixture of both substances is in chemistry called gentian violet, resp. pyoctanine in DAB 6. The name methylic viole is usual, too. Consequently gentian violet, crystal violet, pyoctanine, and methylic violet are equivalent terms of a mixture of penta and hexamethyl-p-rosaniline.

- Chemische Formeldarstellung! -

Hexamethyl-p-rosaniline

Generals

Affected children may have a high colour, frequently, however, they are hollow-eyed, pale and emaciated, short-tempered, i.e. "nervous". The anal itching impairs the necessary attention in school; oxyuriasis may even result in anaemia. The appetite of the child suffering from worms decreases, the sleep is uneasy, due to the anal itching, thus increasing the general

25X1

excitableness. In this way the affection with worms entails a vicious circle upon interruption of which the child will flourish like after serious illness.

The knowledge of the way of life of this persistent parasite itself could result in healing of oxyuriasis the life of one culture of such parasites expiring after 93 days latest. But since the just deposited ovum already within six hours grows up to a pupa capable of invasion such a merely biological therapy is rather difficult. Furthermore the microscopically small ova of oxyuris are whirled through the air together with bed-dust when setting the beds in order in the morning. Another source of infection are the pores of hip-clothing. A fairly successful vermicide therapy with GENTIAVERM, therefore, unconditionally requires at best possible avoidance of reinfections:

1) to brush thoroughly the hands always after steels, prior to any repast, and especially after getting up in the morning. The nails must be cleaned in running water i.e. during washing;
2) to wear, for restraining infections by body-linen, tight slips which have to be changed day by day, and soaked in hot water of min. 80°C. Wigand (14) recommends to wear, in addition, a salved swab which is to a small extent inserted into the anus. In this way the migration of the worms, and the oviposition connected with this is prevented, and, at the same time, the danger of the scattering of ova of oxyuris is obviated;
3) to control the environment of the carrier;
4) to remove ova adhering to fruits, salad and vegetables by washing the food in running water since, otherwise, the ova swimming on the water-level in certain circumstances may adhere to the food again.

Indications

Infections caused by oxyuris vermicularis L. (enterobius vermicularis).

Contraindications

All diseases accompanied by delayed relief of the bowels, particularly pyloric stenosis, gastroptosis, gastric dysbasia.

Virtues and Effect

The dye-stuff preparations not requiring any dietetic precautions nor affecting the patient's professional activity such drugs for vermination are perceived as extremely agreeable medicaments. Also as adjuvants neither laxatives nor enemata are required. The sugared GENTIAVERM-pills are protected from the digestive activity of gastric juice by a special coat, thus preventing any premature decomposition of the dye-stuff which, however, is not achieved unless upon strict adherence to rules of application.

The extraordinarily difficultly absorbable dye-stuff is resorbed by the body but to a very small extent, and eliminated again through the kidneys in form of leucobase. The elimi ted dye-stuff, however, cannot be proved unless upon treatment of the urine with oxidising agents, and, therefore, it is not able to appear spontaneously. Almost the whole quantity of biocatalyst remains in the intestine staining the worms in an intensive, violet manner, and killing them at the same time. The adversaries of dye-stuff therapy frequently contest this fact without taking regard to the part the concentration of the dye-stuff in the faecal matter is playing, of course, in this connection. The dosage of GENTIAVERM amounting to 0.06 grams per pill secures a therapeutically effective concentration if simultaneous attention is paid to the fact that an excessive filling of intestine during the cure, as occurring when taking food rich in slime, will counteract on the therapeutic effect. The dye-stuffs contained in GENTIAVERM are almost completely eliminated together with stool.

The prominent effect of the dye-stuff preparations when treating oxyuriasis is proved by the examinations of Schmidt and Mendheim (9) who attended 84 children, and report on their successes. As found by controls executed under use of the diagnostically very exact sticking-tape of cellophane after first treatment 71.4 percents, and after second treatment 94 percents of the children were free from worms.

Application and Dosage

Generally a 3 days' treatment with GENTIAVERM is provided. In especially tenacious cases the therapy may be continued for some further days, or the treatment is repeated after an interval of a fortnight.

Upon the clinical tests carried out on our GENTIAVERM the following scheme of dosing may be recommended for a 3 days' treatment:

Children up to 3 years old . . . . . daily 1 pill,
Children aged from 3 to 10 years . . . . twice a day 1 pill,
Children aged more than 10 years . . . . thrice a day 1 pill,
Adult and children aged more than 15 . . thrice a day 2 pills.

It is of utmost importance to medicate GENTIAVERM one hour prior to repast together with a drink or with soup since it will take its optimal effect in the intestine if not thinned by chyme.

If the sugared pills are not taken until in the end of repast, and if, in the event of fatty food, they remain in the stomach for a period exceeding 2 hours the pills are decomposed resulting in symptoms of incompatibility on the part of stomach which will appear most distinctly at hyperacidity while a subacid or anacid stomach, according to observations, does not cause any phenomena of irritation. In the event of existing hyperacidity, therefore, it is advisable to medicate from the very beginning and at the same time small quantities of Neutralon so as to bind the excessive hydrochloric acid. Drugs containing bicarbonate of soda and similar alkalizing preparations are not suitable for such purpose as they would even accelerate the decomposition of the pills within stomach.

When adhering strictly to the treatment rules any symptoms of incompatibility are absolutely excluded the coat soluble in the small intestine preventing such troubles.

Particularly when medicating the sugared pills to children special care should be taken for the drug being swallowed quickly and unchewed. Any sucking should be avoided as the saliva is subject to extended daily variations showing pH-values from 5.0 to 8.5 so that occasionally pH-figures of the intestinal environment may be reached. In this manner the protective coat can be sometimes dissolved in the mouth, too.

Careful adherence to unconditionally required general precautions, as already discussed in details, is of fundamental importance for a successful treatment of oxyuriasis.

In spite of this a cure may remain without success, too. Weleker (13) points out that oxyuriasis of the appendix never is to be considered as insignificant, secondary state since the appendix in case of disordered conveyance of stool may become, at the same time, a reservoir of worms. In such, frequently even pathological cases after treatment, of course, worms are continuously discharged from the appendix, thus pretending a failure of the vermicide. Such cases must occur also when using other preparations. Even ferment-drugs must fail in such event!

In case of need appendectomy should be thought of. In this connection is further to be noticed that worms in the appendix may cause symptoms similar to appendicitis; even marked, toxic forms of worm-appendicopathia capable of developing even lymphangitis oxyurica are observed.

It is clear that such tenacious cases cannot be remedied but by total elimination of any re-infection, i.e. by appendectomy; but, nevertheless, also after enucleiresis two treatments with GENTIAVERM are still required. Conclusion: the ideal patient is quite in a position to cure his oxyuriasis without any medication of drugs; but since we have to reckon with the feible of men GENTIAVERM should be taken for treatment of verminations.

Original packing

20 sugared pills of 0.06 grams each.

Clinical packing

250 sugared pills of 0.06 grams each.

25X1

[redacted]

25X1

ATTACHMENT TO [illegible] 11/11

F

PERMAEMYL FORTE

Highly Concentrated Liver Preparation

Containing 20γ of Vitamine B_{12} per Ampoulle

P E R M A E M Y L F O R T E

Highly Concentrated Liver Preparation containing 20 of vitamine B_{12} per ampoulle

Physiology of Pernicious Anaemia

Our liver preparation PERMAEMYL FORTE is closely connected with pernicious or Biermer's anaemia. Prior to diving into particulars as to the drug itself we have to thrash out in detail the features of this illness.

Biermer's disease is characterized by excessive destruction of red blood cells together with disturbed riping and output on the part of bone-marrow resulting in an advanced and dangerous reduction of the circulating quantity of red blood cells. This is why in climax of this disease a reduction o the absolute number of red blood cells is found entailing severe consequences; on one hand the quantity of oxygen received does not meet any longer the body's demand, on the other hand the bilirubin of serum is increased, due to intensive splitting of haemoglobin, bilirubin, the bile pigment, being the final product of reduction of haemoglobin. Besides stercobilin is eliminated in enormous quantities. This matter causes the typical colour of steels; it is closely akin to the urobilin, elimination of which is increased, too, entailing a dark colour of urine.

From this discrepancy between reproduction and destruction of erythrocyts the pernicious aspect results. Remarkably oppo d to the small quantity of reticulocytes within circulating blood the anatomic state of bone-marrow shows extended erythroblastic centres appearing occasionally also within milt and liver.

Instead of nucleus-less, normal (normoblastic) erythrocytes at times of fully developed disease the type of abnormally large and frequently nucleated megaloblasts is regenerated, i.e. big cells rich in haemoglobin which, afterwards, are found as hyperchromic macrocytes within peripheral blood, too. Therefore the colour index is more than 1. For this reason the illness is called hyperchromic anaemia, too.

The megaloblasts the marrow of hollow bones is filled with show a remarkably low tendency to differentiation and ripening. The bone-marrow is of inferior hyperplastic and simultaneously

 SECRET

acting quality. From this the paradoxical feature results that, the poorer the peripheral blood is in red cells, the more the bone-marrow is filled with blood-forming particles.

The substantial feature, therefore, is the disturbed ripening process of the cells of bone-marrow; the supplied cells are of inferior acting quality and fall soon a victim to haemolysis.

Besides this hindrance of formation of normal erythrocytes in case of pernicious anaemia also the metabolism of haemoglobin is suffering from qualitative disorder; within blood-serum, furthermore, besides bilirubin also haematin is found. (We remember that haemoglobin consists of globin, the albuminous body, and haematin, the chromatophore.) The Megaloblasts, furthermore, develop small quantities of porphyrin, a red-violet dye-stuff forming, together with iron, the haemin. (In general the salts of haematin are called haemin.) Increased quantities of porphyrin appear within stools and urine.

This whole and severe pathological condition of disordered ripening and blockage of bone-marrow, increased haemolysis and qualitative disorder of metabolism of haemoglobin is remedied at once by the supply of fresh liver or liver extract.

Biological Elements of Liver Therapy

Since its publication, i.e. since 30 years, Castle's theory concerning the nature of pernicious anaemia has been acknowledged, saying that the patient suffering from this disease is not able any longer to form by himself the Intrinsic Factor developed within the stomach cells adjacent to the pylorus, and within Brunner's cells of the duodenum. Besides a general lack of ferments seems to be existent; even hydrochloric acid and pepsin are missing. Histamin-refractory achilia appears prior to or in parallel with the outbreak of pernicious anaemia. the atrophy of stomach lining encroaches also upon the lining of duodenum and oesophagus. Occasionally polipous deteriorations of gastric mucosa are found tending, in the event of existing pernicious anaemia, more than otherwise to maligmant degeneration.

The intrinsic factor is formed by liver preparations which synthesis the sound body but not the patient's organism is able to carry out.

SECRET 25X1

25X1

Pernicious Anaemia as Avitaminosis

In this way the independent pernicious anaemia in shape of megalocytic, hyperchromic anaemia is characterized, among others, by hypofermentia, resp. afermentia; according to Castle the intrinsic factor permits to resorb the haematopoietic vitamin from food. In this manner the pernicious anaemia is an avitaminosis arising in case of stopped gastric secretion. This is why the metabolism of cells within marrow is disordered: the cells become unable to differenciate themselves and to ripen. Since there is a lack of functioning erythrocytes mesenchymal bone-marrow cells are hastily issued, thus also resulting in the pathological anatomic picture of red marrow, the hyperplasia of marrow. Such mesenchymal, adolescent bone-marrow cells, however, are perishing, due to their unripened condition, prematurily, thus being not capable of normopoiesis. The same disorder is simultaneously true as to the nucleusless bone-marrow cells (myelopoiesis and thrombopoiesis). Therefore it is actually a kind of panmyelophthisis with preponderant symptoms of the red train. The cells of inferior quality and perishing prematurily are eliminated. The oversegmented leucocytes are successively old, and the thrombopenia entails haemorrhages which can be occasionally found on the eye-grounds, but also on the skin.

History of Liver Therapy

In general opinion the liver therapy has been discovered by Minot and Murphy. We are prepared to acknowledge that these two researchers have made well-known the liver therapy, thus finally putting aside the fright at Biermer's anaemia (so called to the honour of the physician Biermer of Breslau) entailing, up to that time, nearly always a fatal outcome.

Discussing shortly the history of liver therapy it seems practical to regard the development backwards from our days.

In 1934 the Nobel-prize of Medicine was carried off by Minot, Murphy and Whipple, due to their liver therapy of pernicious anaemia.

In 1912 Pietro Castellino and Pirera cured pernicious anaemia with liver. Therefore the Consiglio Nazionale adjudged to them the priority of liver therapy of pernicious anaemia.

25X1

In 1911 the well-known German pediatrist Czerny recommends, on occasion of a pediatrists' meeting in Paris, the treatment of anaemia with liver, and reports even on remedial successes.

In 1898 Engel recommends in the German weekly "Deutsche Med. Wochenschrift" to cure anaemia with liver.

In 1880 Sir Patrick Manson, the discoverer of sprue, used to medicate liver extract for anaemia. He reports that he owes his therapy to the Chinese who father it upon Confucius.

From 551 to 478 b.Chr. Confucius lived, the earliest, proved author of the liver therapy. Probably this therapy is much older.

The rediscovery of the liver therapy in 1926 by Minot and Murphy was basing on a discovery of the American Whipple who observed at exsanguinated dogs a considerable acceleration of regeneration when feeding them with raw liver. Minot and Murphy transferred this statement to patients suffering from pernicious anaemia thus achieving their striking successes though the matter in question at the dogs were bleeding anaemias and Whipple certainly succeeded only due to the fact that raw liver happens to contain much iron. The next year, in 1927, the liver therapy was introduced in Europe.

In the beginning 250 grams of raw liver had to be given per day. Such high daily doses entailed soon the patients' dislike resulting in vomiting the medicated liver, thus preventing any therapeutical success. Fulfer (23), therefore, recommended a rectal therapy with liver squash. Although he believes in successes achieved in this manner this can be hardly thought of since, as we know to-day, the vitamin B_{12} is not resorbed within the lower intestinal sections, and, therefore, the effectual substance of the liver, due to which the action on pernicious anaemia really takes place, is eliminated again without any utilisation. In spite of considerable quantities of vitamin B_{12} contained in every one's stools pernicious anaemia may arise.

Liver Extracts

Now the development changed very soon into obtaining the active substances from the liver in order to medicate them parenter-

25X1

ally. In this way the liver extracts, and consequently also our Permaemyl have been developed which, later-on, has been considerably reinforced by further purification in respect to its contents of effective matters receiving then the name PERMAEMYL FORTE.

Lechner and Hirsch (14) report already in 1928 in the weekly "Münchener Med. Wochenschrift" on a liver extract for treatment of pernicious anaemia called "Permaemon". The first study concerning Permaemyl was published in 1933 by Singer (26) in the weekly "Wiener klin. Wochenschrift". In 1934 the weekly "Deutsche medizinische Wochenschrift" published a summary on new drugs stating the Permaemyl, too.

The dry residue of the extracts used now nearly exclusive contains 50 percents of carbon, 6.5 percents of hydrogen, 15 percents of nitrogen, traces of iron and copper, no fats, no carbohydrates, and no pyrimidine-circle.

The proved extract matters consist of guanosine, peptide, tryptophane, tyrosine, xanthopterine.

As to the injectable drugs the extract of about 10 grams of raw liver takes the same effect as the medication of 250 grams of raw liver per os.

Stomach Wall Preparations

In 1930 the Americans Wilkingson, Isaaks and Sharpe discovered that also stomach wall preparations preferably produced from stomachs of pigs achieve same successes as liver preparations. Lombardi (15) checked this statement and reported in the same year in the "Deutsche medizinische Wochenschrift" on successes achieved also by him when using organic substance of stomachs of pigs for therapeutical treatment of pernicious anaemia; this therapy, however, could not pass through.

Extrinsic and Intrinsic Factor

It is true that we know to-day rather exactly why pig's stomach and also the stomach lining of other beasts must act on pernicious anaemia. The stomach lining namely contains the so-called intrinsic factor development of which fails in presence of pernicious anaemia. Therefore the patient suffering from this disease is not able to resorb any longer the extrinsic factor supplied together with food. This is why the intrinsic

factor must be fed perorally in order to get the extrinsic factor resorbed within the digestive tract; on the other hand, however, the extrinsic factor must be fed, of course by parenteral medication only, too, if successful effects are expected. On peroral medication this factor is not effective unless upon simultaneous feeding other resorption promoting matters, e.g. folinic acid.

The Folinic Acid

Within recent years the therapy of pernicious anaemia has considerably progressed since folinic acid has been discovered to contain a couple of other substances acting antianaemically, too.

Vitamin B_{12}

In 1948 the vitamin B_{12} was precipitated from liver in form of a red, crystalline substance taking agreeable effect on haematopoiesis. It contains cobalt and withstands, without being destroyed, temperatures of 120°C. This matter is water-soluble and found in liver, fresh fish, white and yolk of eggs, whey, soyflour, horse-excrements, cow-droppings and also in stools of sound men. A study reporting on the possibility of treatment of pernicious anaemia with human excrements is actually known.

The vitamin B_{12} is called cyanocobalmin, too. It is identical with Castle's dietetic or extrinsic factor.

According to Kjerulf-Jensen and Kerr (11) this vitamin B_{12} is highly sensitive to electric light. This knowledge is, if proved, of enormous importance surely explaining in many events the so-called inefficiency of the liver extract.

In case of pernicious anaemia this vitamin entails a remission of symptoms of this disease; not only deteriorations of blood and marrow disappear but also the nervous phenomena of degeneration are mended. About 5 to 15 gamma per day are medicated by intramuscular injections. For funicular myelosis firstly 40 gamma, later-on 20 gamma are recommended.

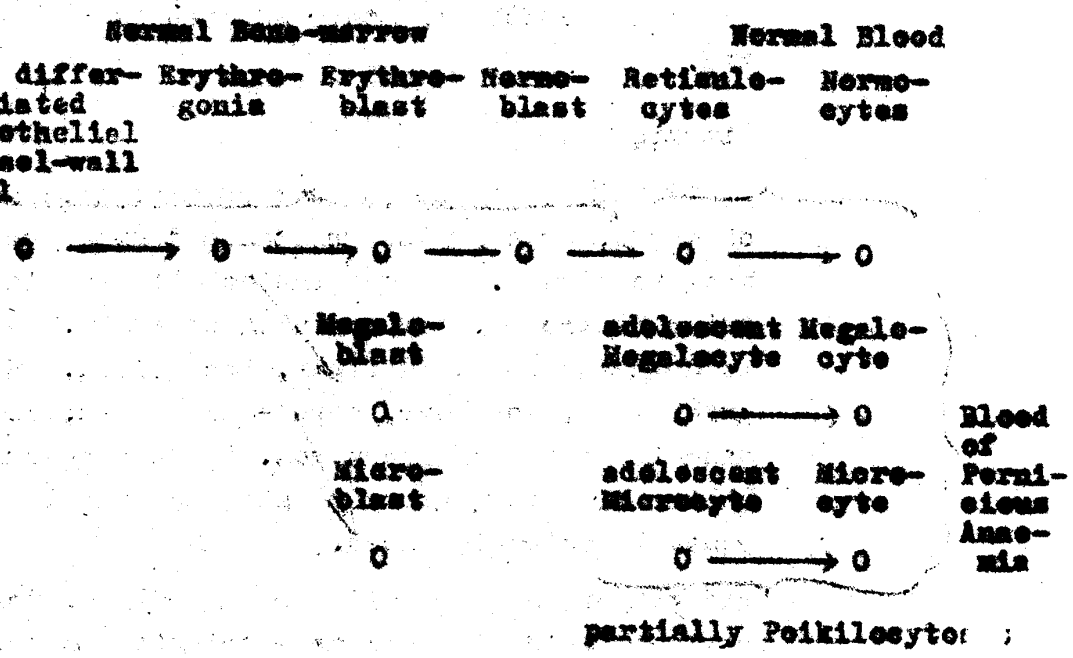
Lately vitamin B_{12} is obtained from the substratum of cultures of streptomyces griseus.

Dyke and his co-operators managed to isolate ample quantities of B_{12} from horse-excrements when examining it after the

25X1

ordure having passed the ileococcal valve. As to human beings they arrived at the same establishment concluding that vitamin B_{12} results from the bacterial flora existing in lower intestine; that means the existence of a bacterial synthesis which, however, is not of any physiological importance since this vitamin B_{12} unfortunately is not resorbed by the rectum. Otherwise any pernicious anaemia would be quite impossible as even could be proved that the important vitamin B_{12} is arising in the intestine of patients suffering from pernicious anaemia, too.

DEVELOPMENT OF THE RED BLOOD-PICTURE



Risc of Avitaminosis

The close relation of vitamin B_{12} to the principle of the anti-pernicious liver effect is now proved. It is a fact that the efficiency of liver extract increases according to the increasing contents of vitamin B_{12}, thus supporting the presumption that pernicious anaemia is a matter of avitaminosis.

In this respect the matter of question may be:

1) Offered food is lacking in vitamines.
2) Lack of capability of elimination on the part of organism.
3) Disordered resorption.
4) Excessive demand, e.g. during gravidity.

There are already present numerous studies concerning partially

BLOOD-PICTURE AT PERNICIOUS ANAEMIA

The value of hemochrom the individual red blood corpuscle is charged with is higher than the normal figure.

Erythrocytes ..... reduced very much
Haemoglobin ..... reduced not so much
Colour index ') ... increased
Furthermore existing:
Aniscocytosis
Poikilocytosis
Polychromasia
Special feature:
Hyperchromic macrocytosis

Mikro-Abbildung!

') = Haemoglobin (in %) / 5 x Erythrocytes (in 100,000)

---

quite long-lasting therapies with vitamin B_{12} which in any case took excellent effect on the blood-picture itself, and never caused, on the contrary to liver preperations, any by-effects or allergic symptoms; but for the present we do not renounce the liver therapy as, in spite of all good success achieved with vitamin B_{12} in regard to the moulting of blood itself, this vitamin is not yet finally proved to own same effect on complete involution of myeloid symptoms and some lingual symptoms as liver with its convenient efficiency.

The study by Aschkenazy and Pariente (2) proves, after all, that the liver extracts contain, besides vitamin B_{12}, at least one further haematopoietic factor, and that the B_{12}-molecule must contain two physiologically different factors one of which can be replaced by methionine. The experiments were given to rats. The research for vitamin B_{12} already resulted in finding four different vitamines B_{12}, namely B_{12}a) to d), each of them owning different properties.

Pernaemyl forte

Now we come back to our special subject: PERNAEMYL FORTE.

Lacks of Provisions

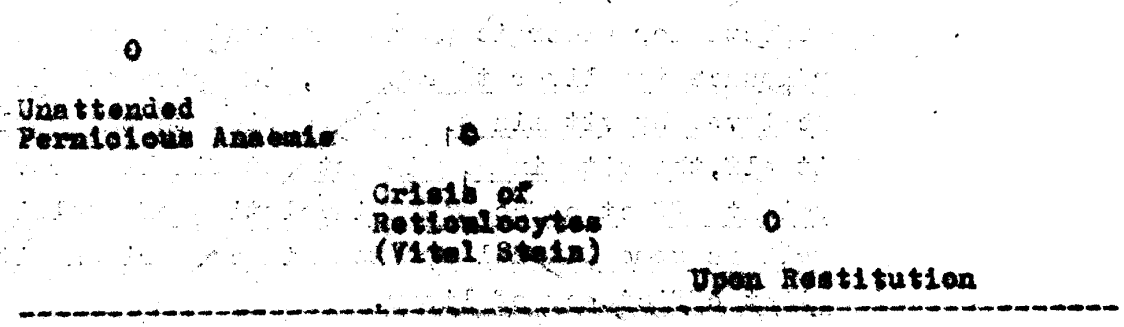
1) Lack of iron. At any treatment of anaemia iron, of course, is playing an important part since it is in any case required for the formation of hemochrome, the haemoglobin. If, however, when curing pernicious anaemia, the iron-store within the organism is completely exhausted and no care is taken for the supply of iron naturally even the liver therapy must remain

25X1

quite long-lasting therapies with vitamin B_{12} which in any case took excellent effect on the blood-picture itself, and never caused, on the contrary to liver preparations, any by-effects nor allergic phenomena; but for the present we do not renounce the liver therapy as, in spite of all good successes achieved by vitamin B_{12} with a view to the moulting of blood itself, the vitamin B_{12} is not yet finally proved to own equivalent effect on complete involution of myeloid symptoms as well as some funicul symptoms in comparison with the convenient efficiency of liver.

BLOOD-PICTURE AT PERNICIOUS ANAEMIA

IMPROVEMENT OF THE BLOOD-PICTURE BY PERNASMYL FORTE



ineffectual. It must be thought, on any condition, of the abnormal, high supply of iron required for the therapy of pernicious anaemia though the matter in question is a so-called hyperchromic anaemia in case of which, when untreated, the iron-level is abnormally high. This is due to disordered erythropoiesis; therefore prior to treatment the demand for iron is low. The serum level of iron, however, intensively decreases very soon after the beginning of the liver therapy the iron now being used, to a larger extent, for synthesis of haemoglobin. The haemoglobin-values are frequently normal already during treatment while the serum figures of iron still remain low, indicating that the iron stores of the body are not yet completely filled up and, therefore, the iron therapy must not be stopped too early.

2) Lack of albumin. Of course also the albumin required for formation of blood is playing a certain part when curing the pernicious anaemia. Moeller (18) was able to prove that in the event of longer lasting malnutrition a distinct crisis of reticulocytes does not set in in spite of liver medication. He interprets this failing, regular crisis of reticulocytes as a lack of albumins required for erythropoiesis.

3) Lack of vitamin B_{12} within liver extract. The insufficient efficiency of liver extracts mainly results from other reasons. Wollin has reported on this fact in a comprehensive study. In 1950 he found that in America for permanent treatment of pernicious anaemia a liver extract quantity of 2 c.cm per month was sufficient while in England considerably higher extract quantities were required then at the same time in USA and also during the prewar years in England. (Even in our country similar conditions were prevailing!) In series of tests 51 patients were treated with different English liver

SECRET

quite long-lasting therapies with vitamin B_{12} which in any case took excellent effect on the blood-picture itself, and never caused, on the contrary to liver preparations, any by-effects nor allergic phenomena; but for the present we do not renounce the liver therapy as, in spite of all good successes achieved by vitamin B_{12} with a view to the moulting of blood itself, the vitamin B_{12} is not yet finally proved to own equivalent effect on complete involution of myeloid symptoms as well as some linguel symptoms in comparison with the convenient efficiency of liver.

BLOOD-PICTURE AT PERNICIOUS ANAEMIA

extracts, and 28 patient with one American drug. The group treated with English preparations did not show any sufficient haematological and clinical remission in spite of the circumstance that since 1943 the medication of increased doses had begun, while the American drug entailed throughout optimal remissions. All patients were similar as to nourishment, age, and social origins. In the author's opinion the reason for this deviation is probably basing on a smaller contents of vitamin B_{12} of the English drugs in comparison with the American ones. The English drugs, however, being subject to continuous clinical tests, too, from such facts the insufficiency of the clinical testing of liver extracts resulted. Now such tests are unobjectionable.

Considerable reactions can be already achieved, at low level of erythrocytes, with proportionally small doses which, however, will not entail full remission. Small doses of thyreoidin encourage the formation of blood!

Summary and Practical Results

Since the pernicious anaemia, in Germany described for the first time by Anton Biermer in 1868, has lost its fright by discovering its causative factors and introducing the liver therapy many researchers aimed at replacing the peroral fresh liver therapy with all its disadvantages by an effective and well compatible injection drug. The PERNAEMYL brought out in 1930 by the German Association for Scientific Organ and Hormone Preparations (Degewop = Deutsche Gesellschaft für wissenschaftliche Organ- und Hormonpräparate) shortly afterwards has been improved to

PERNAEMYL FORTE.

To-day PERNAEMYL FORTE is available as a highly concentrated and reliably acting drug for curing hyperchromic anaemia, which is forgoing free from irritating ballasting matters.

Composition

PERNAEMYL FORTE contains the antipernicious factor of the liver in highly concentrated form, and is set free, by a special procedure, nearly completely from not specific irritants. Allergical symptoms and longer lasting pains at the place of injection, therefore, to-day occur very seldom.

The special features of PERNAEMYL FORTE are:

quite long-lasting therapies with vitamin B_{12} which in any case took excellent effect on the blood-picture itself, and never caused, on the contrary to liver preparations, any by-effects nor allergic phenomena; but for the present we do not renounce the liver therapy as, in spite of all good successes achieved by vitamin B_{12} with a view to the molting of blood itself, the vitamin B_{12} is not yet finally proved to own equivalent effect on complete involution of myeloid symptoms as well as some lingual symptoms in comparison with the convenient efficiency of liver.

BLOOD-PICTURE AT PERNICIOUS ANAEMIA

High efficiency at good compatibility

Any charge of PERNAEMYL FORTE is prior to its delivery tested by leading clinics as to efficiency and compatibility.

Besides any charge is examined as to pyrogenic (toxic) and other ballasting matters.

In PERNAEMYL FORTE the contents of vitamin B_{12} is adjusted to a constant value: PERNAEMYL FORTE contains, besides all other native biocatalysts of the liver required for a successful therapy, 20 gamma of vitamin B_{12} in one ampoulle of 2 c.cm.

It is, according to Harrisen, microbiologically tested with escherichia coli.

Indications

Pernicious anaemia (Biermer's disease) in any stage,
Hyperchromic, megalocytic anaemia (sprue etc.),
Secondary anaemia (anaemia of pregnancy, anaemia of bothriocephalus, at severe gastric diseases and extensive partial gastrectomy),
Hypochromic anaemia (besides iron!) upon blood-losses, particularly after gynaecological haemorrhages, infections, intoxications,
Alimentary anaemia of suckling infants and babies (pseudopernicious infantum, goat's milk anaemia),
Recuperation,
nervous irritation of different organs due to X-rays.

Virtues and Effect

Superior efficiency
due to the contents of antipernicious biocatalysts of liver and vitamin B_{12}.

Simplification of therapy
for physicians and patients.

When medicating PERNAEMYL FORTE the number of injections is reduced to minimum figures.

Exact dosage
due to constant contents of biocatalysts.

Economic medication
due to high efficiency and prolongation of intervals of injections.

25X1

quite long-lasting therapies with vitamin B_{12} which in any case took excellent effect on the blood-picture itself, and never caused, on the contrary to liver preparations, any by-effects nor allergic phenomena; but for the present we do not renounce the liver therapy as, in spite of all good successes achieved by vitamin B_{12} with a view to the remaking of blood itself, the vitamin B_{12} is not yet finally proved to own equivalent effect on complete involution of myeloid symptoms as well as some lingual symptoms in comparison with the convenient efficiency of liver.

BLOOD-PICTURE AT PERNICIOUS ANAEMIA

25X1

Typical syndrome of pernicious anaemia:

Sallow paleness of skin (anaemia of bilirubin!)
Hunter's glossitis in pernicious anaemia
Hyperchromic, megalocytic blood-picture
Central-nervous disorders

is mostly mended, at correct dosage, quickly and continuously nearly up to complete healing. The histamine-refractory achilia is not mended, requiring continuous medication of peptic hydrochloric acid. Already after 4 to 7 days a clear crisis of reticulocytes sets in, and in further course of treatment with PERNAEMYL FORTE the figures of erythrocytes and haemoglobin increase. In some cases the curve of restitution "stops" after initial, prompt amendment whereat the erythrocytes are proportionally poor in haemoglobin. A "combined treatment" using Ferrostabil (4 to 5 times 2 pills per day) will shortly remove this condition indicating the insufficiency of the iron stores for the stormy regeneration of blood. The continuous supply of peptic hydrochloric acid, yeast, uncooked food and rich rye-bread are suitable to reduce the frequency of injections.

While glossitis and gastro-intestinal troubles recide with the amendment of blood-picture <u>for restraining already existing disorders of the central-nervous system (funicular myelosis) the longer lasting medication of higher doses is required.</u>

At all other diseases listed in the index of indications <u>Permaemyl Forte</u> takes the same quick and reliable effect.

Hypochromic anaemias in first line need the iron therapy; PERNAEMYL FORTE, however, in the event of many kinds of this illness clearly intensifies the restitution.

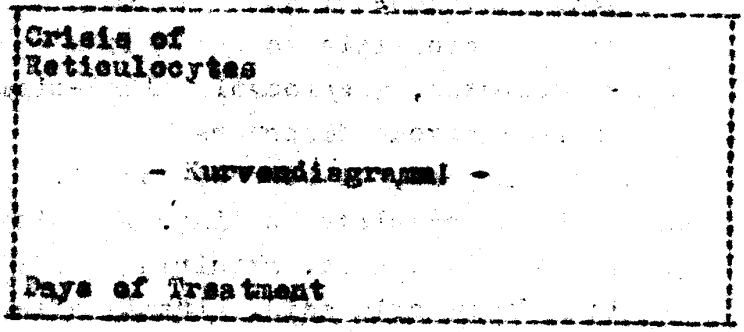
<u>Application and Dosage</u>

The height of dosis, anyhow, depends on the clinical picture whereat the quantity of erythrocytes may be taken as a guide.

When the erythrocytes increased, under treatment, up to at least 3 millions the injections of 2 ampoulles of 2 c.cm each should be continued for further two weeks. For maintenance in most cases a dose of 1 to 2 ampoulles per month will be sufficient; the patient, however, must be kept under permanent medical control.

25X1

25X1



Curve of Restitution upon Medication of Pernaemyl Forte

PERNAEMYL FORTE is suitable for intramuscular injection only.

It is practicable to warm the ampoulle up to body-temperature. The injection should be executed deeply intragluteally (upper exterior quadrant of glut. max.). When injecting correctly under use of a long, pointed and not too thin bore needle the injection will not cause any local phenomena of irritation worth mentioning. Even at very sensitive patients local anaesthetics can be mostly neglected.

Ample consumption of raw or at the least fresh vegetables or fruits considerably supports the recuperation, prevents relapses and saves injections.

Original Packing

3 ampoulles of 2 c.cm each.

Clinical Packing

24 ampoulles of 2 c.cm each.

25X1

Next 1 Page(s) In Document Denied

we have to warn because of the application of SUPRACID in the event of petty diseases (cp.this page herebelow).

Indications

SUPRACID is suitable for treating any disease sulphonamides are indicated for.

Infections through pneumococcus, staphylococcus, and streptococcus.

Bactarium coli, the germ of bacillar dysentery.

renal injuries nor cyanosis, otherwise frequently ensuing the medication of sulphonamides, could be observed.

Stemmermann and Händel (20) as well as Ehlert (4) lay special stress upon the cholelytropic effect reporting on good success as to feverish diseases of the bile-ducts.

Wagner and Bäz (6) report on successes achieved when treating severe, septic diseases of endocardium and lung in case of which penicillin and streptomycin alone did not succeed.

Klecker (11) achieved impressive, extraordinarily comprehensive successes in the line of pediatry. SUPRACID promptly succeeds in defervescence even of penicillin-resistant pneumonias; even mastoiditis is preserved from breaking down, i.e. from operation. In 600 cases tendency to vomit is observed now and again only, impaired appetite seldom, but, on the contrary to this, pronounced good appetite very often. The curves of infantile weight mostly show normal rise. Alkalizing is used only seldom but attention is paid to ample supply of fluid. Cyanosis or haemolytic anaemia are not found but at suckling babies within the first weeks of their life, i.e. at a time where the baby's kidneys and liver are still in state of functional immaturity, and, therefore, of restricted capability of elimination. In this connection the dosage which, in comparison with the adult, is relatively high plays an important part as, with a view to the body-weight, the 3 to 4-fold dose of grown up people is given to the suckling baby. If occasional difficulties should be met when medicating SUPRACID to babies within the first weeks of their life we recommend to prescribe, in case of suitable indication, our Chloramphenicol.

In the line of surgery all infections caused by staphylococcus or streptococcus excellently respond to the medication of SUPRACID.

25X1

NOFORN

Application and Dosage

Similar to all sulphonamides the treatment should be started with full dosage in order to achieve the therapeutically effective, high level of blood, liquor, and tissue as soon as possible.

This is necessary as a subliminal dosage may result in cultivation of sulphonamide-resistant strains (cp. page 3). The superior efficiency of SUPRACID, however, may lead away to its frequent and, in consequence of the superior effect, only short-time application. We herewith beg to warn of the use of sulphonamides for petty diseases as there is the danger of immunity in the event of sulphonamides being medicated oftentimes, even in large intervals of time. With other words: the repeated medication of sulphonamides to the same patient conceals the risk that finally sulphonamide will not take any effect at all. The excellent compatibility, on the contrary, permits the application of highest doses in severe cases.

Upon setting-in therapeutical effect (defervescence) the SUPRACID-cure should be continued for further 3 or 4 days so as to give time enough to the bacteriophags and leucocytes to destroy the paralysed bacteria; in this stage the daily dose may be gradually reduced. Premature stop of medication results in immunisation against sulphonamides.

In most cases an initial dose from 5 to 6 grams = 10 to 12 tablets per day will be sufficient. Upon set-in effect this dose may be reduced to 4 grams = 8 tablets.

In serious cases the initial dose may be increased up to 12 to 15 grams = 24 to 30 tablets per day. In such cases it may be advisable to support the perenal therapy by injections. In this manner, besides, any compatibility on the part of the stomach (occurring, however, very seldom) is avoided.

Proposals of Dosage

Indications	Dosage
I) Angina Bronchitis Cholecystitis Enteritis Erysipelas Furunculosis Impetigo contagiosa Pleuritis Pneumonia Pyelitis Dysentery Cystitis	In the beginning 5 to 6 grams = 10 to 12 tablets per day, later-on 4 grams = 8 tablets every 3 to 4 hours, distributed all over the day. The interruption of the night-rest of eight hours at the highest is not required. In serious cases dosage according to II)
II) Pulmonary abscess Meningococcal meningitis Osteomyelitis Septic diseases	Up to defervescence 8 grams = 16 tablets per day, in equal intervals distributed over day and night, subsequent reduction of doses, but no less than 6 grams per day.
III) Pediatry Upon set-in action the stated doses should be reduced! Owing to the proportionally very high dosage in pediatry special care should be taken for increased supply of fluid!	To suckling babies up the 6th month of their life 0.1 to 0.2 grams/kg of body-weight are medicated per day whereat the number of erythrocytes and the contents of haemoglobin should be continuously tested; both values must not decrease, cp. p.11-12. Suckling babies aged more than 6 months of body-weight up to 10 kgs receive per day 0.4 grams/kg of body-weight.
As to indications see section I) hereabove.	For children up to the 14th year of their life the initial dosis should be rated to 0.2 to 0.3 grams/kg of body-weight. The total quantity per day is not to exceed 8 grams

Contraindication

In case of renal insufficiency any treatment with SUPRACID is contraindicated. If a renal disorder should not belong to the past very long ago the urine has to be examined every day. At the appearance of erythrocytes or albumina in the urine the medication of SUPRACID must be stopped at once.

Practice showed that the therapy with SUPRACID need not be accompanied by increased supply of fluid in any case.

25X1

But it is recommended, nevertheless, in order to avoid, as much as possible, complications even in cases of reduced capability of elimination. If high doses are medicated the additional application of bicarbonate of soda is advisable. SUPRACID may be given through intravenous injections, too. Therefore SUPRACID is particularly indicated in case the peroral medication cannot be carried out.

It is necessary to know, during medication of sulphonamide, the diet poor in vitamine B and yeast (pale Berlin beer, fresh yeast) vitamine B and, in this manner, also yeast advancing the p-aminobenzoic acid in the bacterial body.

Since the peroral medication of sulphonamide considerably affects the vital intestinal flora it is practicable to e. grenate, upon finished medication of sulphonamide, the redevelopment of the intestinal flora by partaking of unscalded food.

Original Packings:

Tube of 20 tablets of 0.5 grams each.

Pasteboard box containing 5 ampoulles of 10 c.cm of 20 percent aqueous solution (as sodium salt) each.

Clinical Packings:

Glass of 500 tablets of 0.5 grams each.

Pasteboard box containing 50 ampoulles of 10 c.cm of 20 percent aqueous solution (as sodium salt) each.

25X1

NOFORN

SECRET

25X1

ATTACHMENT TO EGB — 11/11/2

A

Schering

Ampoulles of Calcium Thiosulphate

"Schering"

Stabile 10 Percent Solution

- TECESAL -

VEB SCHERING ADLERSHOF

NOFORN

SECRET

25X1

Schering

Ampoulles of Calcium Thiosulphate "Schering"
Stabile 10 Percent Solution

- T E C E S A L -

Generals

Calcium is a vital mineral constituent of organism. The total store of calcium within the human body amounts from 0.7 to 1.4 percent of the body-weight. Out of this 99 percents are contained in the skeleton as the calcium deposit of the body while a considerable part of the remainder is found in the blood plasma owning normally a concentration of calcium of 10 mg percent. Calcium being continuously eliminated through kidneys and intestine the permanent supply of calcium is irremissible. The daily requirement for calcium of grown up people amounts to about 0.5 to 1 gram. The demand of pregnant women, however, and during lactation is considerably higher. On basic metabolic condition, particularly in case of achilia, the intake of calcium together with food is disturbed so that this state can be justly designed as osteomalacia achilica.

If the demand for calcium of the body is not met by food the mobilisation of calcium from bones will start. This may cause pathological conditions as appearing, in the event of insufficient nourishment, in form of famine osteopathy.

The metabolism of calcium is controlled by the hormone of the parathyroid glands hyperfunction of which increases the calcium level of blood up to 25 mg percent in case of Recklinghausen's ostitis. Hypofunction of the parathyroid glands, on contrary, is decreasing the calcium level of blood causing so-called hypocalcaemia appearing clinically in shape of tetany caused by the removal of the parathyroid bodies.

Not only the calcium-contents of blood but also the quotient potassium : calcium, which normally should be equal to 2, is decisive for making a diagnosis. A prependerance of calcium as possible in case of acidotic metabolic state will excite the sympathetic nerve. An increased quotient $\frac{K}{Ca}$ is found on vagotonic conditions of anaphylactic shock and bronchial

asthma. Decreases of the quotient accompanied by increasing of the calcium values may cause violent psychical excitement.

The $\frac{K}{Ca}$-quotient influences the morphological blood-picture, too, since preponderance of calcium will increase and that of potassium decrease the number of leukocytes.

The features of an illness appearing in consequence of disturbed metabolism of calcium can be very manifold. Impoverishment of calcium during gravidity and lactation results in osteomalacia-like osseous changes (dental caries). This impoverishment of calcium may result from lack of vitamine D, insufficient supply of calcium, hypofunction of parathyreid glands or from increased demand for calcium during gravidity or lactation.

The removal, respt. atrophy of the parathyreid glands may entail an extraordinarily lowered calcium-level of blood and, in this manner, tetanic spasms, due to the special importance of calcium for the function of nerves.

Together with the washing out of leukocytes from bone-marrow caused by overvalued effect of calcium also the vital activity of particular leukocytes, before all their phagocytosis, is favoured while, at preponderance of potassium, the phagocytosis is stopped.

Allergic diseases being frequently accompanied by vagotonic conditions of the vegetative nervous system calcium is acting antiallergically, too.

Another effect of calcium consists of an elimination of cell-partitions making it suitable for curing illnesses accompanied by disturbances of permeability, occurring in the event of some infectious diseases and all exudations.

Calcium is, besides, a necessary factor for blood-coagulation acting, therefore, antihaemorrhagically at various kinds of haemorrhage.

The thiosulphate-component of thiosulphate of calcium is of mild thio-group effect, intensifies the antiallergical effect of calcium and acts as antagonist at some intoxications particularly those caused by heavy metals.

25X1

25X1

Chemistry and Pharmacology

TECESAL is a 10 percent solution of thiosulphate of calcium according to chemical formula $CaS_2O_3 \cdot 6\ H_2O$.

- Chemische Formeldarstellung -

Thiosulphate of calcium is obtained by replacing the H-ions at the hydroxyle- and sulphhydryle-group by Ca.

- Chemische Formeldarstellung -

Thio-sulphuric Acid

Thiosulphate of Calcium

One ampoulle of TECESAL contains 10 c.cm = 154 milligrams of calcium, i.e. its contents of calcium is essentially higher than that of other preparations. Calcium gluconate = $Ca(C_6H_{11}O_7)_2$ f.i. contains only 9.3 percent of calcium. TECESAL; therefore, is by 70 percents richer in calcium than calcium gluconate.

- Diagramm! -

TECESAL contains 15.4 percents of calcium in 1 gram of substance while gluconate of calcium owns a contents of 9.3 percents of calcium only.

Tecesal Ca-gluconate

Venkeusel and Kimmig (19) managed to prove that, upon injection of TECESAL, the calcium-level of blood rises much quicker and achieves considerably higher values than upon injection of gluconate of calcium. After 25 minutes about one third of the injected calcium-quantity is still found within the blood. The calcium-level of blood decreases slowly down to standard figures in course of 3 to 4 hours. The urine-Ca-level is upon medication of TECESAL doubled or tripled and returns to standard figures within about 2 hours. The elimination is finished 6 hours after injection.

Aqueous solution of thiosulphate of calcium is rather unstable and easily decomposed into therapeutically ineffectual calcium sulphite and into elementary sulphur. TECESAL presents a stable, aqueous solution free from decomposing admixtures and withstanding, without any decomposition, a two hours' sterilisation at 80°C. In pharmacological respect TECESAL is of extremely manysided effect by stopping:

1) Inflammation and exudation,

2) Allergosis,
3) Haemorrhage,
4) Tetany,
5) Intoxication.
6) It acts positively on the skeleton-system.

Owing to such manifold effects the range of indications for parenteral calcium-therapy is very large.

Indications

1) All chronic and acute infectious diseases, particularly tuberculosis, pneumonia, pleurisy, pericarditis, inflammations of liver and bile-ducts, hepatitis epidemica, hydrarthrosis, oedema, exudative diathesis, prophylactically for avoidance of postanaesthetic pneumonia.

2) Anaphylactic phenomena upon serum injections, vagotonic conditions with hypersensibilation, hay-fever, urticaria, asthma bronchiale.

3) Haemorrhagecus diathesis, internal haemorrhages (stomach, intestine, lungs, uterus, kidney), haemorrhage in connexion with abortion, operative and traumatic haemorrhages.

4) Rachitis, osteomalacia, osteoporosis, embryonic maldevelopments and hindrances to growth within the skeleton-system, in case of increased demand for calcium during gravidity and lactation.

5) Tetania, spasmophilia.

6) Intoxications by heavy metals and chemicals, especially hydrocyanic (prussic) acid, autotoxical troubles upon burns by heat or chemicals, intoxications by morbific agents.

Contraindications

Take care at simultaneous medication of digitalis (summation-effect)!

Take care when medicating combined Tecosal-injections (danger of formation of sulphureted hydrogen)!

Combined Tecosal-mercury-injections are incompatible.

Virtues and effect

Among the numerous calcium-drugs TECOSAL excels in its particularly high contents of calcium. This calcium, besides, is con-

25X1

ditioned in high ionisation just the calcium-ions being of biological efficiency. TECESAL contains, furthermore, the extraordinarily important calcium-component causing the advantageous effect of the thiosulphate-component because of which TECESAL, besides the pure calcium-effect, is able to act, moreover, bactericidally, detoxicatingly, highly antiallergically, and to bring about diuresis. TECESAL excels in best compatibility. The warm feeling resulting from an insignificant vascular reaction when TECESAL is injected is harmless and can be reduced by possibly slow injection. If, on the contrary, any perception of heat fails to come during injection this may point out to affected vascular elasticity, and support, at older patients, the presumption of a sclerotic vascular disease.

Calcium is of similar effect on the heart like digitalis so that simultaneous medication of both drugs may cause a summation releasing, under certain circumstances, unagreeable by-effects. Hegeng (13), therefore, even suggests an interval of four days prior to parenteral meditation of calcium upon use of digitalis.

Vaudagna (11) successfully prevented, by application of TECESAL, postanaesthetic pneumonia resulting, in his opinion, from nasal detriments. The noxines arising in course of any operation in consequence of destruction of vessels attack the capillary walls, thus affecting the permeability of their membranes. The lungs owning the most close-meshed capillary network within the human body it is clear that especially distinct and disturbing effects of the noxines will take place in this part. To meet prophylactically the noxines' damaging effect on the capillary membranes of lungs v.Ondersa recommends to meditate upon operation for a period of 4 days 2 x 10 c.cm of TECESAL per day, thus achieving reduced permeability of cellular walls and foregoing avoidance of formation of the albuminous exsudate within interstice and air-cells. In this way the nutrient substratum is taken away from ins. existing germs. The noxines are of optimal efficiency between 2nd and 5th day after operation, i.e. within the same period as anaesthetic pneumonia is appearing which, therefore, for

NOFORN

SECRET

25X1

good reasons is to be considered as moral detriment. Wieher (21) joins this opinion, too, and prefers prophylactical application of TECESAL upon operations which cause considerable destruction of vessels.

Toll (22) successfully carried out a calcium-therapy in case of hepatitis epidemica and reports on remarkably quick recession of clinical phenomena such as icterus and swelling of the liver, on surprisingly quick decrease of bilirubin, on Takata-/re-reaction becoming a negative one very soon, on soon return of appetite, and on mend of general condition. Even in severe cases no failures could be observed. When injecting the drug once a day in average 10 to 12 injections were required.

Sroka (15) recommends, now as ever, TECESAL for therapy of intoxications by heavy metals. It proved especially in the event of poisoning by arsenic, lead (lead-colic), mercury, thallium and bismuth. In case of such severe intoxications TECESAL has become an important antidotal factor. The metallic proteinous compounds bound within the vascular cells are made soluble again by means of thiosulphate, and eliminated through the kidneys in shape of inocuous, thiosulphuric salts.

Rudolphi (14) brings into prominence the good successes of TECESAL when curing lues since in this case it turned out best for prophylaxis against salvarsan-complications. When treating lues, therefore, mixed injections of TECESAL and salvarsan are recommended. Beware, however, of other mixed injections, due to reasons already mentioned (endangering by development of sulphurated hydrogen)!

Also in the event of poisoning with phosphorus and hydrocyanic acid TECESAL has been successfully applied, and, equally to that, also in case of poisonings with phenol as may occur not only as industrial disease but also in consequence of overdosed medication of antitoxic sera with phenol added. Upon application of sulphhydryl the elimination of phenol through urine is increased. The detoxication of hydrocyanic acid is basing on the development of relatively little poisonous hydracid of sulphocyanate. The detoxicating effect of TECESAL may be of importance for children after excessive partaking

25X1

of stones of stone-fruit. Upon massive poisoning with hydrocyanic acid, however, any therapy would come too late, due to the soon effect of this acid.

Roesler (12) recommends a calcium-vigantol-cure in case of vegetative troubles manifesting in extraordinarily manifold symptoms such as: angioneurotic headache, liability to nausea, vasomotory rhinitis, hay-fever (pollinosis), gastric, intestinal and bile-duct spasm, nervous night-sweat, bronchial asthma, angioneurotic oedema, liability to chilblains, urticaria, liability to eczema, non-toxic cardiac and circulatory complications of adolescents, vasomotory stenocardia, thyrotoxicosis and tetanoidal phenomena.

For curing pulmonary tuberculosis calcium has turned out best, too. Voellmy (17) recommends, in the event of pleural effusions, a high-dosed calcium-therapy, and mediates 20 to 40 c.cm daily. When applying this therapy he was able to state a light course of pleurisy with effusion.

Also van den Velden observed that, upon intravenous medication of calcium, reaccumulations of pleuritic effusions after needling can be sometimes avoided; the same is true as to the feared expectoratic seroса. Feucht (5) calls TECESAL the calcium-drug of selection for the treatment of haemoptisis.

Curschmann (4) particularly points out good success when curing renal and vesical haemorrhages.

Wittmaack (9) brings into prominence the manifold possibil y of application of calcium in the special line of diseases of throat, nose and ears. He reports on partially excellent successes in the event of all kinds of the vasomotorily involved Ménière's syndrome, and at inflammatory oedema of larynx, at acute laryngitis and sinusitis, in case of infantile diphtheria with stenosed respiration as well as spasm of the children's glottis. He also recommends to apply calcium prophylactically prior to operations within nasopharynx, in order to prevent inflammations.

Application and Dosage

TECESAL should be mediated only through intravenous injections For avoidance of subjective troubles TECESAL is to be injected

SECRET NOFORN 25X1

very slowly, i.e. 10 c.cm within not less than 5 minutes. Beware of so-called mixed injections TECRSAL being occasionally of bad compatibility with other drugs and decomposing itself whereat sulphurated hydrogen may arise.

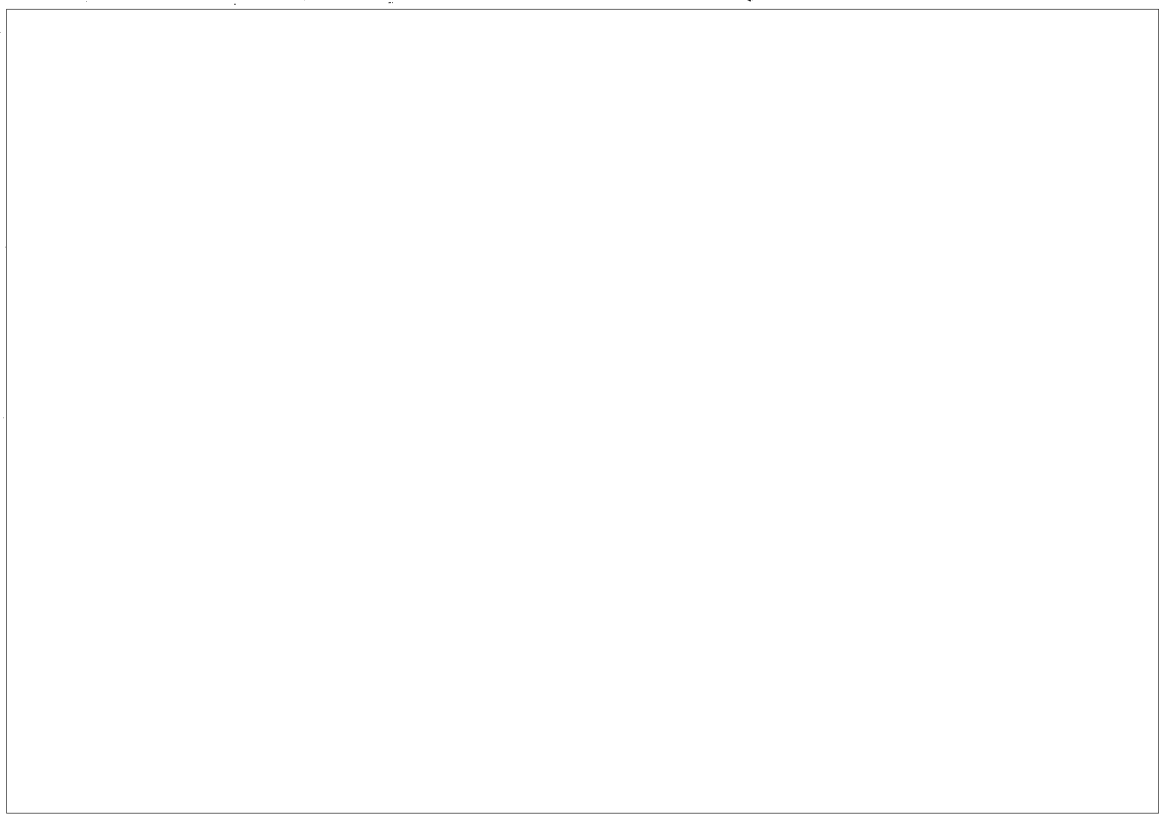
The contents of the ampoulle should be warmed, immediately prior to injection, to body-temperature. Dosage depends on indication. Generally one or two injections will be sufficient. In special cases, however, f.i. in the event of intoxications, considerably higher quantities, up to 5 ampoulles per day, may be given.

In pediatry somehow smaller doses are medicated: in case of spasmophilia of suckling-infants and babies about 2 to 3 c.cm per dose, for older children 1/2 to 1 ampoulle except severe poisoning in the event of which dosage should be increased accordingly.

Original packing: 5 ampoulles of 10 c.cm 10 percent solution each.

Clinical packing: 50 ampoulles of 10 c.cm 10 percent solution each.

25X1



ATTACHMENT TO EGD- 11,112

B

A C E T Y L C H O L I N E

**Biocatalyst of the Parasympathetic Nervous System,
Vaso-dilator**

A C E T Y L C H O L I N E.
- S c h e r i n g -

Biocatalyst of the Parasympathetic Nervous System, Vaso-dilato:

Generals and Chemistry

ACETYLCHOLINE has been educed for the first time in 1867 by V.Beaver. Its biological, vaso-dilatory effect, however, have not been recognised earlier than in 1906 by Hunt and Taveau. Loewi and Dale in 1936 thoroughly explored such vasodilatation in fundamental studies due to which they carried off the Nobel-prize. Among others they managed to prove that, if the vagus is stimulated, from the ends of this nerve a matter is discharged injection of which takes similar effect on the heart as a stimulation of the vagus. Already a short time after this "vagal compound" could be identified as ACETYL-CHOLINE.

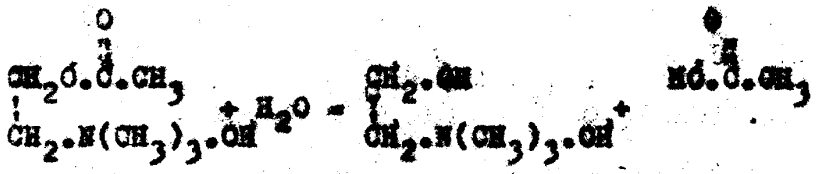
ACETYLCHOLINE lowers the blood-pressure by dilating the small vessels, delays the throbbing of the heart, incites the intestinal peristalsis, and narrows the pupil. It influences the organs in contrary sense to adrenalin. The effect of ACETYLCHOLINE is increased by vitamin B.

Physiologically ACETYLCHOLINE ranges among the neurohormones as it is participating in decisive manner in the release and conduction of stimulations as well as in the transmission of the stimulation from the nerve to the reacting organ.

The quantities of ACETYLCHOLINE eliminated upon a stimulus in the end of a nerve are extraordinarily small. They have been calculated according to Keller (20), and amount to 0.000 000 001 gamma.

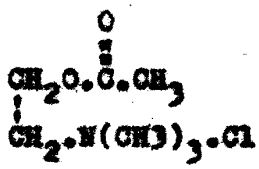
The specific ferment acetylcholinesterase splits the ACETYL-CHOLINE to its two building parts, acetic acid and choline. Choline, playing an important part in metabolism of lipids, takes similar, but much weaker effect than ACETYLCHOLINE. ACETYLCHOLINE acts, in comparison with not esterified choline, on the isolated intestine with 1000-fold, on the blood-pressure with 10000-fold, and on the isolated heart with 100000-fold efficiency.

Physostigmine inactivises the acetylcholinesterase. As physostigmine must not be heated we recommend to replace it in practice by ampoulles of Eustigmine (VEB chem. Fabrik v. Heyden, Dresden-Radebeul). In therapy this effect is playing a considerable part the effect of supplied ACETYLCHOLINE being remarkably prolonged in the event of simultaneous injections of ACETYLCHOLINE and physostigmine. According to Zimnitz (39) this increase of effect relates only to its duration, and not to the intensity. The prolongation of the effect of ACETYLCHOLINE is traced back to the reduced speed of saponification.



Acetylcholine Choline Acetic Acid

ACETYLCHOLINE - Schering - is the very easily water-soluble muriate of ACETYLCHOLINE.



Chloride of Acetylcholine

According to Ratschow's (24) examinations the sympathetic system and, at the same time, also the acetylcholinesterase can be hampered by Jenacain (VEB Jenapharm) resulting in prolongation of the effect of Acetylcholine upon medication of ACETYLCHOLINE at the same time.

Owing to the high sensivity of ACETYLCHOLINE and its quick disintegration by the acetylcholinesterase it is required to carry the ACETYLCHOLINE as near as possible to the very spot of affection. Upon remote medication it would arrive at the seat of affection in foregoing inactivised condition.

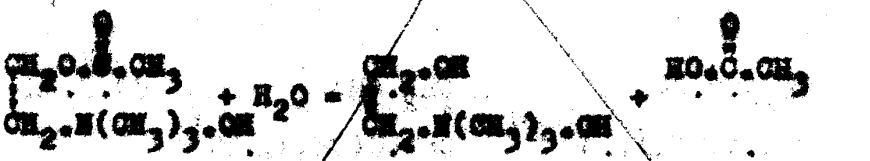
Ismarish (17) was able to prove that ACETYLCHOLINE takes but short-time effect on the heart against to which the vessels remain dilated for longer time, and that probably in consequence of the vaso-motor centre being hampered.

Indications

ACETYLCHOLINE as a body-own hormone is of excellent suitabilit;

25X1

Physostigmine inactivates the acetylcholinesterase. As physostigmine must not be heated we recommend to replace it in practice by ampoulles of Eustigmine (VEB chem. Fabrik v. Heyden, Dresden-Radebeul). In therapy this effect is playing a considerable part the effect of ACETYLCHOLINE supplied being remarkably prolonged in the event of simultaneous injection of ACETYLCHOLINE and physostigmine. According to Zimmig (30) this increase of effect relates only to its duration, and not to the intensity. The prolongation of the effect of ACETYLCHOLINE is traced back to the reduced speed of sapenification.



ACETYLCHOLINE is the very easily water-soluble

to dissipation of vasoconstrictive conditions, and Incitement of the parasympathetic system. Therefore its range of indication is extraordinarily manifold.

Internal medicine: acro paresthesia, intermittent claudication, endarteritis, certain kinds of hemicrania, Raymund's gangrene, paroxismal tachycardia, stimulation of function of bone-marrow, poliomyelitic paralysis, cerebral thrombosis

Surgery and Orthopaedy: Ankylosis (posttraumatic and postoperative), arthrosis deformans, infectious arthritis, muscular hardness and paralysis, paralytic ileus.

Dermatology: Acrodermatitis atrophicans, frostbites, ulcer of the leg, varicose ulcer.

Ophthalmology: Chemical burns, herpes of cornea, ophthalmic hemicrania, spasm of retinal arteries.

Special line of cervical, nasal, and aural diseases: Anaesna, hussing in the ears, giddiness.

Neurology: Paralysis.

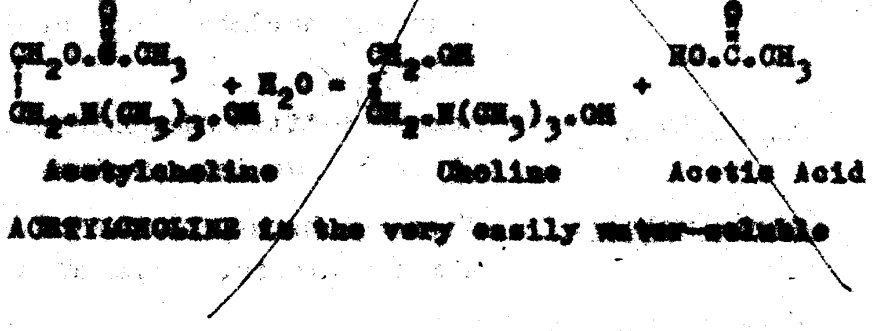
Virtues and Effect

ACETYLCHOLIN may be called an antagonist of the adrenalin. Its effect on the organs is contrary to that of adrenalin. Consequently it dilates the vessels, slows down the throbbing of the heart, thus also lowering the pressure of blood. Also the frequently appearing arteriospasms are relieved, thus dissipating disorders of blood-supply resulting from arteriospasm. Wherever local disorders of blood-supply are playing a part in connection with abnormal sensations ACETYLCHOLINE is indicated. Ratschow recommends a local infiltration consisting of ACETYLCHOLINE and 1 percent Jenacain whereat 0.1 gram of ACETYLCHOLINE is to be mixed up with 5 c.cm of 1 percent solution of Jenacain, thus supporting the blood-supply encouraging effect of the ACETYLCHOLINE by the action of Jenacain blocking the sympathetic system. Simultaneously the use of this mixture entails a temporal prolongation of the ACETYLCHOLINE-effect Jenacain, similar to physostigmine, arresting the tissue esterase. In the event of any feeling of pain, as frequently playing a part just at indication of ACETYLCHOLINE, the combi-

[redacted]

25X1

tigmine inactivises the acetylcholinesterase. As physostigmine must not be heated we recommend to replace it in practice by capsulles of Dustigmine (VEB chem. Fabrik v. Heyden, Dresden-Radebeul). In therapy this effect is playing a considerable part the effect of ACETYLCHOLINE supplied being remarkably prolonged in the event of simultaneous injection of ACETYLCHOLINE and physostigmine. According to Simnitz (30) this increase of effect relates only to its duration, and not to the intensity. The prolongation of the effect of ACETYLCHOLINE is traced back to the reduced speed of saponification.



Acetylcholine Choline Acetic Acid

ACETYLCHOLINE is the very easily water-soluble

nation with Jemecain takes beneficient effect. Even sharpest pains are eased at once.

Holz and Lohel (16) achieved good success when using ACETYLCHOLINE for treatment of the seredermatitis atrophicans. They report, it is true, on convenient remedial success in case of frostbites and ulcers of the leg but they point out that particulary ulcers resulting from pyodermia are responding well to an ACETYLCHOLINE-therapy.

Stolte (28) managed to remedy disorders of the arterial, peripheral blood-supply by means of intraarterial injections. He succeeded in curing senile arteriosclerosis, diabetic arteriosclerosis, and cases of thrombangiitis obliterans, and that by mixing up 100 mg of ACETYLCHOLINE with 100 c.cm of distilled water, and injecting this mixture within 30 to 40 seconds. Subsequently, within 1 minute after the intraarterial injection, the skin of the part suffering from bad blood-supply got roseate and warm, and began to sweat.

Recently also Krümmel and Popp reported on similar, convenient successes publishing their experiences on the treatment of totally 98 cases of arteriosclerosis, endangiitis obliterans, and Raynaud's disease whereupon they found 66.3 percents of the cases amended essentially while 17.3 percents grew better to a small extent, and 16.3 percents only remained uninfluenced Owing to the simplicity of procedure and the risklessness the intraarterial ACETYLCHOLINE-treatment is recommended to the medical practitioner, too.

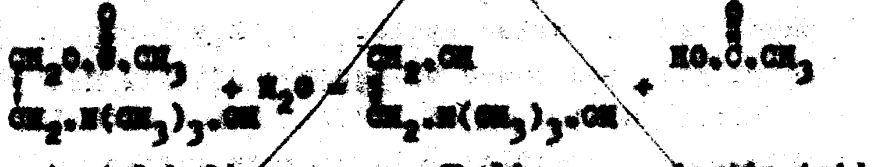
Eitel (11) was able to succeed by medicating high doses in the event of ulcer of the leg, and that in spite of the fugitive peripheral dilatory effect. He injected round the ulcers and every second day 0.3 to 0.6 grams of ACETYLCHOLINE, and reported on their epithelization within 2 to 3 weeks. The histological findings showed intensive vascularization in the area of ACETYLCHOLINE-injections.

Schuler (26) combines, when curing throphic ulcers on the leg, the ACETYLCHOLINE-therapy with medication of vitamin B pointing out expressively that even ulcers which did not respond up to this time to any therapy are tending now to surprisingly quick healing.

Neuburger and Scholl could state on hand of a greater number

25X1

Physostigmine inactivises the acetylcholinesterase. As physostigmine must not be heated we recommend to replace it in practice by ampoulles of Eustigmine (VEB chem. Fabrik v. Heyden, Dresden-Radebeul). In therapy this effect is playing a considerable part the effect of ACETYLCHOLINE supplied being remarkably prolonged in the event of simultaneous injection of ACETYLCHOLINE and physostigmine. According to Simnitz (30) this increase of effect relates only to its duration, and not to the intensity. The prolongation of the effect of ACETYLCHOLINE is traced back to the reduced speed of saponification.



Acetylcholine Choline Acetic Acid

ACETYLCHOLINE is the very easily water-soluble

NOFORN 25X1

of cases of arthrosis deformans that such disease can be essentially amended by serial perenteral medication of ACETYLCHOLINE. Out of 35 patients 30 remained permanently free from their former troubles. The therapy consisted of one injection comprising 0.1 g of ACETYLCHOLINE dissolved in sterile water which had been applied every second day.

Payr (23) reports on excellent successes achieved when using ACETYLCHOLINE for the treatment of genuine arthrosis deformans and primary arthrosis deformans. He especially points out that in the great majority of the cases the therapy resulted in success practically without any recurrence. Excessive rumbling noise, crepitation, and grating could not be annulled completely, it is true, but mostly they were grossly reduced. Already after a few treatments the movability was amended to largest extent.

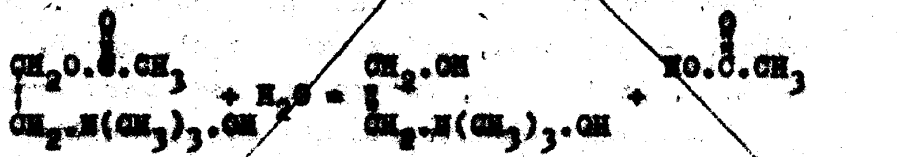
Also traumatic arthrosis and infectious arthritis mostly could be well influenced by ACETYLCHOLINE. Payr reports, furthermore, on good success in respect to muscular stiffening of shoulder.

Olivier (22) injected, at compressed veins, ACETYLCHOLINE into the peripheral stump of tied up arteries observing hereby a quickly starting increase of blood-supply with local rise of temperature in 5 out of 7 cases. He points out that by the compression of veins disturbing variations of blood-pressure are avoided, and that, however, an addition of Jenacain in such cases had proved unsuitable.

Good success achieved with ACETYLCHOLINE could be stated in connection with paroxismal tachycardia. While according to V. Kiss (18) the pulse is slowing down within 26 minutes from 186 to 86, and the blood-pressure is normalized at the same time, according to Fischer (12) in 3 cases the tachycardia was improved immediately after injection.

Bogatski (4) ascertained, upon injections of daily 100 mgs of ACETYLCHOLINE into muscles, increased figures of thrombocytes and reticulocytes, mostly also of erythrocytes and haemoglobin in any case, concluding from this a stimulation of the function of bone-marrow by the ACETYLCHOLINE. He even points out that ACETYLCHOLINE proved superior to iron-therapy. He reports on 20 clinical cases, and that on 15 hypochromic anaemias partiall essential and partially subsequent to infections, resp. cancer, 4 essential thrombopenias, and 1 case of normal blood-picture

Physostigmine inactivises the acetylcholinesterase. As physostigmine must not be heated we recommend to replace it in practice by ampoulles of Eustigmine (VEB chem. Fabrik v. Heyden, Dresden-Radebeul). In therapy this effect is playing a considerable part the effect of ACETYLCHOLINE supplied being remarkably prolongéd in the event of simultaneous injection of ACETYLCHOLINE and physostigmine. According to Zimmitz (30) this increase of effect relates only to its duration, and not to the intensity. The prolongation of the effect of ACETYLCHOLINE is traced back to the reduced speed of saponification.



Acetylcholine Choline Acetic Acid

ACETYLCHOLINE is the very easily water-soluble

NOFORN RELEASABLE

SECRET

subject to medical attendance, due to intermittent claudication. Danielopolu and Braunar (9) also report on soon increase of erythrocytes and reticulocytes as well as simultaneous improvement of clinical symptoms upon treatment with ACETYLCHOLINE. Even anisocytosis and poikilocytosis disappeared in consequence of this treatment, and that by subcutaneous or intramuscular application of an initial dose from 0.02 to 0.08 gs, i.e. the initial dose of 0.02 gs was increased up to 0.08 gs. From experience this dose could be increased, without any troubles, even to 0.12 gs. It is particulary brought into prominence that ACETYLCHOLINE was acting even in case of liver-extract and stomach lining preparations failing. It is recommended, however, to medicate iron additionally.

For paralytic ileus ACETYLCHOLINE was successfully used, too. Heritage (15) recommends an infusion of 1/4 to 1/2 litre of normal saline solution with 5 percent of glukose applied by intravenous injection together with intramuscular injection of 0.2 gs of ACETYLCHOLINE, and, subsequently, three times 0.1 g of ACETYLCHOLINE each in intervals of one hour. Abel (2) advises on the medication of injections of 0.1 g of ACETYLCHOLINE every 6 hours, and that after 36 hours upon any abdominal operation, up to flatus, resp. movements.

Also in the line of ophthalmology ACETYLCHOLINE has turned out best. Dejean (10) managed to interrupt seisures of ophthalmic hemicrania within a few minutes by intramuscular injections of 0.1 g of ACETYLCHOLINE. Haselmann and Pulfrich used ACETYLCHOLINE for treating chemical burns of the eyes; in intervals from 5 to 10 minutes they dripped a 5 to 10 percent solution into the conjunctiva until all injured part of conjunctiva showing convenient supply of blood. Marchesani treated herpes corneae with ACETYLCHOLINE and prostigmin; the disease healed quickly since the herpes-virus interferes the chemism of nervine metabolism and probably behaves similar to cholinesterase because of which even a causal therapy is effected by ACETYLCHOLINE.

In the special line of cervical, nasal, and aurel diseases ACETYLCHOLINE is recommended for treatment of genuine eczema. It is hyperaemising the vessels by dilating them. Most convenient success could be achieved at beginning eczema but also in cases of progressed disease favourable influence could be exercised on the habit of mucosa, foetor, and formation of escher.

Poliomyelitic paralysis also was treated with ACETYLCHOLINE. Strecker (29) and Klare (19) refer but to the possibility of such therapy, it is true, but Cacciputi (6) could state, upon a therapy with ACETYLCHOLINE and tincture of digitalis, an amendment of the symptoms of poliomyelitic paralysis. He medicated 5 to 7 guttae of tincture of digitalis in water in the morning, and injected 3 hours after 0.1 g of ACETYLCHOLINE. In course of treatment the ACETYLCHOLINE-dose was increased up to 0.2 grams. To patients suffering from lack of appetite or constipation Gebhardt (13) daily injected 0.1 g of ACETYLCHOLINE. The general influence was favourable, the appetite grew better, and the obstipation was eased.

Recently ACETYLCHOLINE seems to gain importance also in respect to diagnosis. Becher (3) reports particulary on the examination of Head's zones by means of the ACETYLCHOLINE-physostigmin-test.

In Head's opinion the pains and tegmental hyperalgesia are elicited reflexly according to the segmental innervation of organs, i.e. the pain indicated by the patient does not correspond to the ill spot of the organ. Therefore at the methods of examination used up to now the patients' informations frequently were wrong. For excluding such errors Becher in the event of abdominal diseases examined Head's zones by means of the ACETYLCHOLINE-physostigmin-test.

When proceeding against this objective method of examination 0.2 c.cm of a solution consisting of 5 percent ACETYLCHOLIN + 5 per thou. physostigmin (5:1), which is always mixed up anew, is applied by strictly intracutaneous, wheal-like injections, in 2 fingers' breadth laterally from the spinal processes of the backbone, into the corresponding places of the tegmental regions from D 5 to L 2.

Upon such injections the development of a reflex-erythema is studied as to size, intensity of colour, and speed of appearance. At sound persons it will appear in the corresponding tegmental regions in equal speed, size, and intensitiy of colour while at patients this process is accelerated. In such event, furthermore, the erythema is larger than in adjacent regions, and distinguishes by increased intensity of colour.

According to Becher at such observations the matter in question

is a segmental, reflex vaso-dilation caused by chemical impulses.

Application and Dosage

ACETYLCHOLINE not keeping very long in aqueous solution but splitting itself into chloride of choline and acetic acid ACETYLCHOLINE - Schering - is sold in phials containing it in dehydrated condition. To each ampoulle of 0.1 g of ACETYLCHOLINE belongs an ampoulle of 2 c.cm of sterile, bidistilled water. The durability of the solution of ACETYLCHOLINE lasts, according to present Haeneppel's (14) examinations of ready ACETYLCHOLINE-solutions, one month and a half upon sterilisation through bacterium-arresting filters, appr. one month upon 30 minutes' sterilisation by heating up to 100°C, and 1 to 2 weeks upon 60 minutes' heating up to 100°C. Such figures are true for storing at room-temperature. In the refrigerator the disintegration will run an essentially slower course. This is why the solution of ACETYLCHOLINE is not required to be mixed up just before medication in any case.

The ampoulles are opened, 1 c.cm of the water are for rinsing purposes sucked into the syringe and discharged again. Subsequently 1 c.cm of water are sucked up once more, and injected into the ampoulle of ACETYLCHOLINE which is dissolved at once. The solution is clear and thinly liquid because of which thin needles may be used.

As already emphasized above it is unconditionally required to carry the ACETYLCHOLINE as close as possible to the very spot of affection in order to avoid far extending inactivization by the esterase of ACETYLCHOLINE. Mixed injections with Jenacain or physostigmin increase the effect of ACETYLCHOLINE such admixtures stopping the ACETYLCHOLINE-esterase, resp. blocking at the same time the sympathetic system similar to the effect of Jenacain.

When treating joints Payr recommends to proceed according to the following method: Apply a wheal by injecting a 1/2 percent Jenacain-adrenaline-solution, and anaesthetise the capsule with a 2 to 5 percent solution of Jenacain. After a small pause 0.05 to 0.1 g of ACETYLCHOLINE are injected into the joint-cavity itself; after the injection into the capsule, however, firstly should be ascertained whether the point of the canula

25X1

is correctly inserted into the joint-cavity. Subsequently a little quantity of 2 percent Jenacain-solution more is additionally filled in.

For the application of injections below tissue-parts Hels and Lehal (16) recommend to use the following solution: Upon dissolution of 0.1 to 0.3 g of ACETYLCHOLINE in 2 c.cm of distilled water 25 mgs of vitamin B_1, 0.5 mgs of physostigmin, and 5 c.cm of a 2 percent Jenacain-solution (without adrenalin!) are added and with sterile, bidistilled water thinned to 10 c.cm. This mixture is injected below the affected tissue-parts by means of a long needle.

Finally we beg to point out once more that ACETYLCHOLINE should be injected as close as possible to the seat of illness.

Original Packing:

6 ampoulles of 0.1 g of ACETYLCHOLINE = Schering = each.
6 ampoulles of 2 c.cm of bidistilled water each.

25X1

NOFORN

SECRET

Next 1 Page(s) In Document Denied

ATTACHMENT TO BOB — 11,11 2

C

A L L U V A L

Alpha-bromisovalerylcarbamide

S e d a t i v e

A L L U V A L F O R T E

Alpha-bromisovalerylcarbamide
with Diethylbarbiturate of Sodium

S e d a t i v e

H y p n o t i c

S p a s m o l y t i c

25X1

A L L U V A L / A L L U V A L F O R T E

General:

To the ancient Hellenes and Romans the valerian was known as official drug which they called "phu". Since the 11th century the name "valeriana", to be deducted, according to Linné, from the designation "Baldrian", i.e. the herb of the god of light Baldur, which is usual in Germany and Scandinavian countries, has gained currency. Other authors are tracing back the name to the Roman physician Plinius Valerianus resp. to the Latin word "valere" = to be in good health. In Germany in Middle Ages the valerian-root was known under the name "[illegible]", resp. "[illegible]", too. In some regions of Switzerland such names are used up to now. In pharmacy valerian (valeriana offic.) is playing also nowadays the same considerable part as before. Especially the essential extract from the root is looked upon as an excellent sedative for nervous excitements, and, in second line, also as saperific. As most effective constituent of valerian the isovalerianic acid is mentioned (valerianic acid and valerylic acid are convertible terms).

Already a few years after the discovery of the bromine in the water of the Mediterranean Sea by Balard in 1826 the bromide of potassium was used as medicament. Bromine is quieting the cortex of the central-nervous system, too.

Chemistry and Pharmacology

25X1

Upon small doses of bromine the feeling of ease and debility sets in resulting, upon higher doses, in numbness and tendency to sleep. In this way bromine favours the falling asleep since, as cortex-drug, it attenuates during its action the thinking-power and responsiveness to impulses, thus quieting much occupied thinkers; it protects from brooding and, in this manner, from anxiety. Bromine is hesitantly eliminated and, therefore, of proportionally long-lasting effect while valerian is decomposed in the body rather soon.

Both the bromine, pharmacologically used as halogen and ammonium compound, and valerian, however, are taking unagreeable by-effects valerian owning a smell which is unagreeable for many patients, and bromine being able to cause skin-troubles (rash caused by bromine).

Therefore it was a grateful task for pharmacy to unit the positive effects of the two medical drugs isovalerianic acid and bromine in one medicament eliminating simultaneously the unagreeable by-effects. For this purpose urea was used which, moreover, was already known for the preparation of soporiferous draughts.

In 1863 A.v.Baeyer for the first time educed a ureal soporific, namely the barbituric acid consisting of

(- Chemische Formeldarstellung! -)

Malonic acid + urea ⟶ Barbituric acid (Malonylic urea)

malonylic urea = barbituric acid; as circle-compound it takes proportionally intensive effect, and even at only medium dosage and longer lasting medication we objectively find hepatic injuries and cutaneous deteriorations perceived as itching. On the contrary to the corticotropic bromine the barbituric acid is acting, before all, on the subcortex, and in second line as well as mediately on the cortex itself. The effect on the subcortex entails intensive influence on internal organs. The poisoning with barbitonum is typified by slightly bleeding exudations from stomach and intestinal lining as well as other serous teguments. Longer lasting use of barbituric bodies may affect the intellectual abilities.

The amin-like formed ureal compound, on the contrary to that, is not in a position to deteriorate provably the organs.

(- Chemische Formeldarstellung! -)

Alpha-bromisovalerylcarbamide - ALLUVAL

In 1907, and upon systematic exploratory work the alpha-bromisovalerylcarbamide educed by Sagm could be introduced into the therapy. The capability of this medical drug to keep its rank in therapy for up to now nearly 50 years past is a special proof of its virtues.

The much-felt want for sedatives and soporifics required, after 1945, to restore the alpha-bromisovalerylcarbamide in shape of ALLUVAL. For reinforcing the soporiferous effect of this drug ALLUVAL FORTE has been developed by combining ALLUVAL with 0.03 grams of diethylbarbiturate of sodium.

It is clear that this small quantity of diethylbarbiturate of sodium must not be plainly considered as soporific a dose of 0.03 grams being quite insufficient for producing sleep. Since, however, neurasthenics at sensitive feebleness are easily responding even to slightest impulses even harmless sensations in the body not perceived by a sound man at all may intensify the excitement. Which neurasthenic does not suffer from palpitation of the heart, slightly spasmodic headache, or troublesome, dragging sensation within digestive apparatus? Such troubles, be they perceived in the neurasthenic's heart, head, or abdomen, are caused by slight spasm of vessels or visceral muscles. The small quantity of diethylbarbiturate of sodium suffices for immunizing the subcortex against the said sensations; it is added to ALLUVAL FORTE, and, therefore, ALLUVAL FORTE takes corresponding, antispastic effect.

Alpha-bromisovalerylcarbamide forms white needles of slightly bitter taste, which are soluble in hot water, ether, and alcohol; in cold water, however, the dissolution is difficult. The melting-point ranges between 147 and 149 centigrades (°C), and the substance is easily sublimable.

A dose from 0.2 to 0.25 grams/kg lets a rabbit fall into dead sleep. A dose of 0.5 grams/kg already intensively lessens respiration. Further increase of dosage results in standstill of respiration while the heart goes on throbbing. The lethal dose for a rabbit amounts to about 1 gram/kg.

In therapy the alpha-bromisovalerylcarbamide is not poisonous. Müller (7) in 1911 reported on a woman of 34 years who had tried to commit suicide by imbibing 30 tablets of 0.3 grams each. She slept for 36 hours, and her sleep was fast and equivalent to physiological sleep. Heart and circulation did their normal work, reflexes were existing, sensibility but lessened, and the urine free from abnormal constituents. The patient felt herself refreshed by the sleep, and even a couple of weeks afterwards she was not able to state any bad sequels.

In a study by Jakob (3) even stronger stress is laid upon the harmlessness of the drug. He reports on a patient who regularly took high doses of the drug for 10 years, and that during the first 2 years some tablets in course of day and in the evening additionally 10 tablets of 0.3 grams each, in the last years,

however, he imbibed daily one roll of 20 tablets of 0.3 grams each, occasionally even 30 x 0.3 grams. Such very massive doses, indeed, entailed vertigo and disturbances in gait.

Indications

Owing to their convenient sedative effect ALLUVAL and ALLUVAL FORTE are indicated for all excitements. The drugs have turned out well in the event of:

excitement of any kind, particularly in neurasthenny, pertussis, thyrotoxicosis, climacteric period, for suckling babies during dentition period, and for accustoming to nigh-rest.

We are reciting this latter particulars from literature without adopting them as, in our opinion, the pedagogical accustoming of the suckling baby is the natural procedure for parents and children.

intellectual overwork,
stage-fever,
hysteria,
arteriosclerotic troubles,
neurosis,
sleeplessness of low and medium grade,
air and sea-sickness (prophylactic),
epilepsy, especially of children,
nightmare,
twitching.

Virtues and Effect

The compound of isovalerianic acid and urea warrants the quick splitting of the drug within the body. Then the urea encourages the renal activity and accelerates elimination. A cumulation of the drug, therefore, can be considered as practically excluded, even at longer lasting medication.

By binding the atom of bromine in alpha-position the isovalerianic acid takes sedative effect and acts hypnotically, and simultaneously all by-effects of the bromine are avoided. Even in case of longer lasting medication the appearance of bromism need not be reckoned with.

A special virtue of ALLUVAL is its harmlessness. Even the 10-fold quantity of the therapeutically effective dose, i.e.

6 grams for adult and 1 gram for children, causes but rest and sleep without any secondary phenomena. No suicidal attempt carried out with ALLUVAL has been successful up to now. Also as to ALLUVAL FORTE the maximum single dose of diethylbarbiturate of sodium according to DAB 6 is not reached until 25 tablets are taken. Consequently a suicidal attempt by imbibing 27 tablets of ALLUVAL FORTE must fail, too. This patient even could be roused by shaking him; hence he was not so much as unconscious.

Nor ALLUVAL neither ALLUVAL FORTE are taking similar effect as the other soporifics known up to now. The alluvals are differing from them, in first line, by complete exclusion of any narcotic secondary and subsequent effect. ALLUVAL and ALLUVAL FORTE, therefore, are not only soporifics free from causing any troubles but also effecting, on next day, a well-being nearly verging upon euphoria.

In this connection, of course, one restriction should be made: The patient's uneasiness must not result from pains. It is true that slight headache from vascular spasm in consequence of the excitement, and also clinically insignificant myalgia upon extraordinarily hard intellectual work are eased by this sedative as, together with the intellectual relaxation caused by ALLUVAL and ALLUVAL FORTE, the spasm both of vessels and of muscles is stopped automatically. If, however, the pains are of organic origine the sedative, on the contrary to anodynes (antineuralgics), is not able to expel the troubles. On the other hand the dose of anodyne required for alleviation of pain can be kept small in case the neurasthenic tending to pains is using, besides the anodyne, a sedative, too. This fact is known to such an extent that further details need not be discussed. Hundreds of combination-drugs are proving it enough.

One thing else we would point out: similar to circulatory and some renal diseases also at the neurasthenic the urea of the alluvals takes diuretic effect. In order to avoid the patient being prematurily wakened by urgency of urination, thus preventing their optimal action of the convenient drug, he should desist, when taking ALLUVAL (and, of course, also some hours before), from partaking of diuretical food: tea, coffee, beer, wine, liqueur; large quantities of vegetables, particularly

asparagus, celery-stick, parsley-root, potatoes; instead of these cereals should be preferred.

ALLUVAL in doses of 0.3 to 0.6 grams takes drowsy effect, and quiets for an average period of 3 to 5 hours. After this time the effect ceases, due to the quick reduction of the agent in the body. The dose of 0.9 grams, of course, effects a sleep of 8 hours, and that not for pharmacological but for physical reasons for, in consequence of this ALLUVAL-sleep, the central-nervous system is refreshed to such an extent that it responds, even after the discharge of ALLUVAL into the urinary bladder, to impulses only normally, thus actually enjoying a normal, sound sleep. For this reason also the appr. doubled dose will not take any increased effect. Only from ALLUVAL FORTE an increased effect should be expected, due to the added diethylbarbiturate of sodium. - After awakening from ALLUVAL-sleep the patient will, upon further medication, quickly fall asleep again.

The ALLUVAL-sleep is similar to natural sleep; it is free from dreams. After awakening the patient is conscious, and feels refreshed.

At severe resistance against sleep ALLUVAL is not suitable failing in case of severe unrest, cough, pains, high fever, and delirium. In such event, however, a slightly increased dose of ALLUVAL FORTE may still succeed.

In consequence of the therapeutic application of the alpha-bromisovalerylcarbamide for decades of years past the clinical experiences collected on this drug must be quite comprehensive; numerous publications report on the excellent qualities. In this connection the studies by Krieger, v.d.Velden (4), Bunck, (11) and Mampell (6) should be pointed out for their laying stress upon the convenient soporific effect. Mampell (6) writes that he never failed to succeed in cases of sleeplessness of slightly neurasthenic patients, at agrypnia caused by overwork, or in the event of other nervous conditions. He could observe, on the contrary, the patient's slow and quiet falling asleep within 10 to 30 minutes after the medication of 0.3 to 0.6 grams of the drug; a sound sleep of 4 hours at the least followed very soon, and could be repeated upon taking the same dose. In the great majority of medications the sleep induced by ALLUVAL results in natural sleep not ending before daybreak unless interrupted prematurily by disturbances from outside.

Runck (11) reports on the good effect of the drug in respect to suppression of perspiration. Particularly for inconvenient night-sweats persons afflicted with rheumatism and phthisis are especially suffering from it will pay to try ALLUVAL. Runck recommends for such indication a dose of 0.6 grams which in tenacious cases should be given more than once, and that in intervals from 3 to 5 hours.

Ferrenon and Hoffmann (2) succeeded in curing sea-sickness with alpha-bromisovalerylcarbamide. The drug should be taken possibly prophylactically 1 or 2 hours prior to departure. At rough sea 0.6 grams, taken in the evening, turned out as convenient help for getting over the night. In cases of already existing nausea a single dose from 0.6 to 0.9 grams as able to help at once. The use of ALLUVAL is to be recommended in prophylactic manner also prior to voyages by plane or but short sea-trips.

Schäfer (12) achieved good success when using alpha-bromisovalerylcarbamide in the line of pediatry medicating it particularly in cases of infantile hysteria, epilepsy, nightmare and twitching. As effective dose the application of 0.3 grams each once to thrice a day turned out well. In this connection we beg to remind that we like to consider the neurasthenia of children and babies as a problem of education to be settled possibly without any drugs.

In spite of this Alluval, of course, may be subject to manifold application in pediatry. Mampell (6) reports on advantageous effects on pertussis ALLUVAL reducing the frequency and gravity of the fits of coughing. Mampell medicates to suckling babies aged from 1/2 to 1 year in the morning and in the evening 1/4 to 1/2 tablet each. ALLUVAL can be successfully used also for restless babies as the same dose medicated in the evening and, if necessary, at midnight, will procure the necessary night-rest for the mother without inflicting the least harm upon the child. Similar good effect ALLUVAL takes when used for teething babies.

Also in general practice best use may be made of ALLUVAL, and that particularly upon Schäfer's (12) report that alpha-bromisovalerylcarbamide calms neurasthenia, cardiac and vascular neurosis, angina pectoris, peptic thrills, and sexual alterations, stills pains, and secondary phenomena never were observed.

ALLUVAL and ALLUVAL FORTE do not act narcotically, resp. but to a very small extent. But on the other hand they excel in very intensive, sedative effects, and, therefore, they are the neurotic's indispensable sedative. Owing to this advantageous, sedative effect they have turned out best as sleeping draught for neurotic patients.

Application and Dosage

ALLUVAL is sold in tablets of 0.3 grams each. It is of barely bitter taste, and in this way superior to the valerian-drugs with their unsavoury taste. When swallowing the tablets no taste is perceived. The ALLUVAL-tablets disintegrate quickly particularly in hot water, thus enabling even suckling babies to take them in form of suspension. - It is advisable to prefer this kind of medication to babies in order to prevent the tablets going down the wrong way.

Owing to the admixture of diethylbarbiturate of sodium FORTE ALLUVAL is of light-yellow colour and slight, but not inconveniently bitter taste. It is to be used in cases of maniacal excitement in same doses as ALLUVAL.

At excitement as diurnal sedative:	more than once a day 1 or 2 tablets.
At sleeplessness:	2 to 3 tablets appr. 1/2 hour prior to going to bed.
At night-sweat:	2 tablets prior to going to bed, evtl. subsequently 2 tablets every 3 to 4 hours.
Prophylactically against air- and sea-sickness:	2 tablets prior to departure, in case of impending nausea immediately 2 to 3 tablets with some fluid.

The dosage for children ranges, in dependence on their age, from 1/4 to 1 tablet.

Original Packings

ALLUVAL . . . . . 10 tablets of 0.3 grams each,
ALLUVAL FORTE . . . . 10 tablets of 0.33 grams each.

Clinical Packings

ALLUVAL . . . . . .250 tablets of 0.3 grams each,
ALLUVAL FORTE . . . .250 tablets of 0.33 grams each.